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GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders – First Revision

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Abstract

In this report, which is an update of a guideline published in 2002 (Bandelow et al. 2002, World J Biol Psychiatry 3:171), recommendations for the pharmacological treatment of anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are presented. Since the publication of the first version of this guideline, a substantial number of new randomized controlled studies of anxiolytics have been published. In particular, more relapse prevention studies are now available that show sustained efficacy of anxiolytic drugs. The recommendations, developed by the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders, a consensus panel of 30 international experts, are now based on 510 published randomized, placebo- or comparator-controlled clinical studies (RCTs) and 130 open studies and case reports. First-line treatments for these disorders are selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and the calcium channel modulator pregabalin. Tricyclic antidepressants (TCAs) are equally effective for some disorders, but many are less well tolerated than the SSRIs/SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Potential treatment options for patients unresponsive to standard treatments are described in this overview. Although these guidelines focus on medications, non-pharmacological were also considered. Cognitive behavioural therapy (CBT) and other variants of behaviour therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, OCD, and PTSD to support them being recommended either alone or in combination with the above medicines.

Key words: *Anticonvulsants, antidepressants, antipsychotics, anxiety disorders, anxiolytics, benzodiazepines, cognitive behaviour therapy, evidence-based guidelines, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, simple phobia, social phobia, SSRI, SNRI, treatment*

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Preface and Disclosure Statement

The preparation of these guidelines has not been financially supported by any commercial organization. This practice guideline has mainly been developed mainly by psychiatrists and psychotherapists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to medicines discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest.

Some drugs recommended in the present guideline may not be available in all countries.

Introduction

Anxiety disorders belong to the most prevalent psychiatric disorders, and considerable burden is associated with these disorders, not only for the individual sufferer, but also for the health care system. However, many patients who might benefit from treatment are not diagnosed or treated. This may partly be due to lack of awareness of the anxiety disorders by primary care practitioners. Also, the stigma still associated with psychiatric disorders and lack of confidence in psychiatric treatments are likely factors leading to non-recognition and subsequently to a lack of treatment or the use of unnecessary or inappropriate methods. We hope that this guideline may contribute to an improvement in the management of patients with anxiety disorders.

This guideline represents the first revision of the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-traumatic Stress Disorders, a consensus panel of international experts for anxiety disorders, OCD and PTSD (Bandelow et al. 2002b). Since the first version in 2002, many clinical studies have been conducted and a number of new treatments have emerged. Therefore, the Task Force deemed it necessary to update the guidelines. Further revisions are planned in the future.

This guidance makes recommendations on the management of anxiety, obsessive-compulsive and post-traumatic stress disorders and addresses all healthcare professionals in primary, secondary and community care.

Methods

The present guideline is based on evidence from controlled clinical studies, adhering to the principles of evidence-based medicine. Data were extracted from published articles from the MEDLINE Database and the Science Citation Index at Web of Science (ISI) (until June 2008). A few additional trials were found by hand-searching.

The recommendations are based on studies that fulfilled certain methodological requirements, summarized in Table III (for the quality requirements for RCTs, see also SIGN and Jadad et al. (1996)).

Open studies and case reports have also been collected in order to provide treatment suggestions for patients not responding to standard treatments. They have to be interpreted with much caution because to the strong placebo effect and possible publication biases.

Recommendations from recent guideline activities were also considered (Table I). To be recommended, a drug must have shown its efficacy in double-blind placebo-controlled (DBPC) studies. When an established standard treatment exists for a specific disorder, a drug must have been compared with this reference drug (comparator trial). However, a comparator trial alone without a placebo control is not regarded as sufficient, as there is the risk that inferiority of the new drug to the reference drug may not be detected due to the low statistical power of a study, with large sample sizes needed for the test of equal efficacy. Usually, non-inferiority trials are used, i.e. a trial showing that the new drug is not less effective than the reference drug. In these studies, lower sample sizes are required than in superiority trials. In a non-inferiority trial, the optimal sample size depends on the definition of a clinically meaningful difference, and this definition may be arbitrary. A consensus of experts in the field has evolved regarding the following requirements for a non-inferiority trial (Nutt et al. 2008):

- A placebo arm should be included in order to ensure "assay sensitivity";
- both active drugs should be superior to placebo by an accepted clinically meaningful difference on a specific rating scale (e.g., ≥ 2 points on the HAMA)
- both active drugs should be superior to placebo in terms of response rate ($\geq 10\%$ better than placebo), while response is usually defined as a $\geq 50\%$ improvement on this scale;
- the non-inferiority margin, i.e. the difference between the active drugs on the main efficacy measure (e.g., the HAMA) should be $< 50\%$ of the difference between the reference drug and placebo in previous trials;
- the response rate for the new drug should be no more than 5% lower than for the reference drug;

Table I. Recent Guidelines on the Treatment of Anxiety Disorders, OCD and PTSD

Guideline	Source	Recommended minimum duration of pharmacotherapy
Royal Australian and New Zealand College of Psychiatrists: Australian and New Zealand Clinical Practice Guidelines for the Treatment of Panic Disorder and Agoraphobia	Andrews 2003	No recommendation
World Council on Anxiety: Recommendations for the long-term treatment of panic disorder	Pollack et al. 2003a	12–24 months
– Generalized anxiety disorder	Allgulander et al. 2003	No recommendation due to lack of data
– Social phobia	van Ameringen et al. 2003	12 months
– Obsessive-compulsive disorder in adults	Greist et al. 2003	12–24 months
– Post-traumatic stress disorder	Stein et al. 2003a	12–24 months
Evidence-based Guidelines for the Pharmacological Treatment of Anxiety Disorders: recommendations from the British Association for Psychopharmacology	Baldwin et al. 2005	6 months after initial response to treatment
Canadian Psychiatric Association Clinical Practice Guidelines, Management of Anxiety Disorders	Canadian Psychiatric Association 2006	PD: 8–12 months GAD: no recommendation SAD: 12–24 months OCD: 12–24 months
National Institute for Health and Clinical Excellence (NICE). Anxiety (amended): management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care	NICE 2007	6 months after initial response to treatment
American Psychiatric Association: practice guideline for the treatment of patients with obsessive-compulsive disorder	Koran et al. 2007	12–14 months
National Institute for Clinical Excellence (NICE): obsessive compulsive disorder: core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder.	NICE 2006	12 months or more
National Institute for Clinical Excellence (NICE): Post-Traumatic Stress Disorder. the management of PTSD in adults and children in primary and secondary care.	NICE 2005	12 months or more
Department of Veteran Affairs: post-traumatic stress disorder. clinical practice guidelines.	Veteran Affairs 2007	No recommendation
Institute of Medicine: treatment of PTSD: an assessment of the evidence. Report brief	Institute of Medicine 2007	No recommendation

– the one-sided 97.5% confidence interval of the non-inferiority margin should fall within an *a-priori* defined interval, e.g., 1.5 points on the HAMA.

However, ethical issues of non-inferiority trials are still being debated (e.g., Garattini and Bertele 2007).

Categories of evidence

The categories of evidence used in this guideline are described in Table II. In recent guidelines, different categories of evidence have been applied. When searching for a commonly used grading system of categories of evidence for the guidelines of the WFSBP, we found that there is no generally accepted system for medicinal or psychological treatment interventions. It would be desirable that the same hierarchy of evidence is used in all such guidelines. However, there is a lack of consensus about the optimal grading system. In the literature, we found some problems with existing categories. For example, it was difficult to adopt the categories of evidence used in the UK NICE guidelines (NICE 2007), which were based on a system developed by (Eccles and Mason 2001), due to some methodological issues. These problems are discussed in the Editorial of this issue (Bandelow et al. 2008). Because of these shortcomings of existing grading systems, we decided to develop special levels of evidence for this guideline and other guidelines of the WFSBP series, by integrating suggestions from other guideline activities and by trying to use definitions that are optimally adapted to the situation of evidential data in psychiatry, in order to provide optimal transparency for healthcare providers and patients. The principles of this system are:

1. the first category A is reserved for treatments that were effective in more than one RCT and in comparator trials;
2. meta-analyses are only required when evidence from original data is not sufficient;

Table II. Categories of Evidence. In Table VI, the Categories of Evidence are Given for all Recommended Drugs.

Category of evidence	Description
↑↑ **A**	**Full evidence from controlled studies** is based on: two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) *and* one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies that shows superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfill established methodological standards (Table III). The decision is based on the primary efficacy measure.
↑**B**	**Limited positive evidence from controlled studies** is based on: one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") *or* a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial. *and* no negative studies exist
(↑) **C**	**Evidence from uncontrolled studies or case reports/expert opinion**
C1	*Uncontrolled studies* is based on: one or more positive naturalistic open studies (with a minimum of five evaluable patients) *or* a comparison with a reference drug with a sample size insufficient for a non-inferiority trial *and* no negative controlled studies exist
C2	**Case reports** is based on: one or more positive case reports *and* no negative controlled studies exist
C3	Based on the opinion of experts in the field or clinical experience
↔ **D**	**Inconsistent results** Positive RCTs are outweighed by an approximately equal number of negative studies
↓ **E**	**Negative evidence** The majority of RCTs studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment
? F	**Lack of evidence** Adequate studies proving efficacy or non-efficacy are lacking

Recommendation Grade	**Based on:**
1	Category A evidence *and* good risk-benefit ratio
2	Category A evidence *and* moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

3. the second category B is used for treatments, which have only been studied in one (or more) DBPC trials without comparator;
4. the grading system also contains a category C for data from open studies;
5. comparisons with a reference drug with a sample size insufficient for a non-inferiority trial are treated like open data;
6. a category for "inconsistent data" (D) was introduced;

Table III. Check list for Quality of Controlled Studies.

- Study described as randomized*; method used to generate the sequence of randomization described and appropriate (e.g., computer-generated)*
- Use of standard diagnostic criteria (e.g., DSM or ICD)
- Study described as double-blind*; method of double-blinding described and appropriate* (identical placebo, dummy etc., or use of a "psychological placebo" control and assessment by a "blind" rater in the case of psychotherapy studies)
- Description of withdrawals and dropouts*; declaration of evaluation method ("intent to treat"/"according to protocol")
- In the case of an active comparator: use of a comparator with established efficacy
- The only difference between groups is the treatment under investigation
- Use of parallel groups (instead of cross-over studies, wait list controls or "historical" comparisons)
- Adequate sample size, based on *a-priori* calculation
- Use of sensitive rating scales
- Declaration of the primary efficacy measure
- Use of appropriate statistical tests (e.g., control for baseline differences etc.); method of management of drop-outs described (e.g., last observation carried forward/LOCF, mixed model repeated measures analysis/MMRM)
- Fulfillment of good clinical practice (GCP) criteria
- Approval by properly-constituted ethics committee

*These points are part of the Jadad Score Jadad et al. 1996

7. a difference was made between "negative evidence" (E) and "lack of evidence" (F).

Recommendation grades

These categories of evidence are based on efficacy only, without regard to other advantages or disadvantages of the drugs, such as side effects or interactions; however, these matters are key. Therefore, recommendation grades were also used. For example, the evidence for the efficacy of benzodiazepines is very good (Category of Evidence A), but they are only recommended as second line treatment due to their abuse potential (Recommendation Grade 2). The recommendation grades can be viewed as steps: The first step would be a prescription of a medication with Recommendation Grade 1. When this treatment fails, all other Grade 1 options should be tried first before switching to treatments with Recommendation Grade 2.

In our recommendations, we have not considered the direct or indirect costs of treatments, as these vary substantially across the different health care systems.

These principles of practice are considered guidelines only. Adherence to them will not ensure a successful outcome in every case. The individual treatment of a patient should be planned by the psychiatrist in the light of clinical features presented by the patient and the diagnostic and treatment options available.

Some of the drugs recommended in this guideline may not (or not yet) have received approval for the treatment of anxiety disorders in every country. As the approval by national regulatory authorities is dependent on a variety of factors, this guideline is exclusively based on the available evidence.

Diagnosis

In Table IV, a short overview of the various disorders is given. There is marked overlap among the anxiety disorders and comorbidity with other psychiatric disorders such as depression (Bandelow 2003).

Epidemiology

Anxiety disorders, OCD, and PTSD belong to the most frequent psychiatric disorders. Twelve-months and lifetime prevalence rates from the National Comorbidity Survey Replication (NCS-R), a representative population survey conducted between 2001 and 2003 (Kessler et al. 2005a,b) are shown in Figure 1. According to a comparison with the first National Comobidity Survey conducted between 1990 and 1992, the prevalence of anxiety disorders did not change during the decade, but the rate of treatment increased (Kessler et al. 2005c).

Epidemiological data collected from a variety of countries have documented differences in prevalence rates for the anxiety disorders (Bandelow 2003; Wittchen and Jacobi 2005).

The median age of onset is 7 for specific phobia, 13 for SAD, 19 for OCD, 23 for PTSD, 24 for panic disorder, and 31 for GAD (Kessler et al. 2005a). The anxiety disorders tend to disappear in the fifth decade (Bandelow 2003; Kessler et al. 2005a; Rubio and Lopez-Ibor 2007a, b).

Patients with anxiety disorders are frequent users of emergency medical services (Klerman et al. 1991; Wang et al. 2005), are at a high risk for suicide attempts (Weissman et al. 1989) and at risk for substance abuse (Brady and Lydiard 1993). Costs associated with the anxiety disorders represent

Table IV. Short description of anxiety disorders as defined by ICD-10 (WHO 1991) and DSM-IV-TR (APA 2000)

Panic disorder (PD)
Panic disorder is characterized by recurrent panic attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least four of 14 somatic and psychic symptoms (13 in DSM-IV). A panic attack reaches a peak within 10 minutes and lasts 30–45 minutes on average. Usually, the patient is afraid that he has a serious medical condition such as myocardial infarction.

Agoraphobia
About two-thirds of all patients with panic disorder suffer from agoraphobia, which is defined as fear in places or situations from which escape might be difficult or in which help may not be available in the event of having an unexpected panic attack. These situations include being in a crowd or standing in a line, being outside the home alone, or traveling in a bus, train or automobile. These situations are avoided or endured with marked distress.

Generalized anxiety disorder (GAD)
The main features of generalized anxiety disorder are excessive anxiety and worry. The patients suffer from somatic anxiety symptoms as well as from restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances and being easily fatigued. Patient may express constant worry that the patient or a relative will shortly become ill or have an accident.

Specific phobia
Specific phobia is characterized by excessive or unreasonable fear of single objects or situations (e.g., flying, heights, animals, seeing blood, etc.).

Social phobia (social anxiety disorder; SAD)
This disorder is characterized by marked, persistent, and unreasonable fear of being observed or evaluated negatively by others in social performance or interaction situations and is associated with somatic and cognitive symptoms. The feared situations are avoided or else are endured with intense anxiety or distress. These situations include fear of speaking in public, speaking to unfamiliar people or being exposed to possible scrutiny by others.

Obsessive-compulsive disorder (OCD)
OCD is characterized by recurrent obsessions or compulsions, or both, that cause impairment in terms of distress, time, or interference with functioning. Concerns involving contamination, harm, hoarding, and sexual, somatic and religious preoccupations are the most common obsessions. Compulsions include washing, checking, repeating, ordering, counting, hoarding and touching (rare).

Post-traumatic stress disorder (PTSD)
Post-traumatic stress disorder (PTSD) develops after a terrifying ordeal that involved physical harm or the threat of physical harm. The person who develops PTSD may have been the one who was harmed, the harm may have happened to a loved one, or the person may have witnessed a harmful event that happened to loved ones or strangers. The condition is characterized by recurrent and intrusive distressing recollections of the event, nightmares, a sense of reliving the experience with illusions, hallucinations, or dissociative flashback episodes, intense psychological or physiological distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, inability to recall important aspects of the trauma, loss of interest, estrangement from others, sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response. The full symptom picture must be present for more than 1 month.

approximately one-third of the total expenditures for mental illness (DuPont et al. 1996; Rice and Miller 1998; Wittchen 2002). In primary care, anxiety disorders are often underdiagnosed (Sartorius et al. 1996) or recognized only years after onset. Frequently, clinicians fail to take advantage of available effective treatment strategies (Bandelow et al. 1995; Cowley et al. 1997).

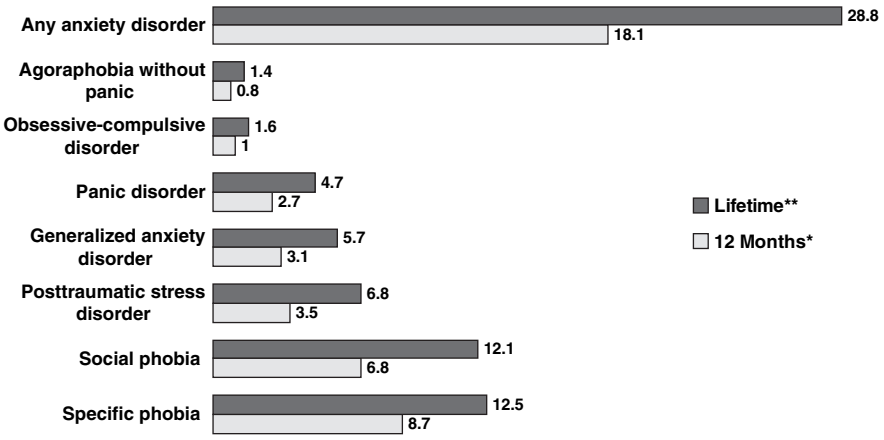

Figure 1. Anxiety Disorders, OCD and PTSD. Twelve-month and lifetime prevalence rates. Data from the National Comorbidity Survey Replication. *Kessler et al. 2005c; **Kessler et al. 2005a.

Aetiology

Hypotheses on the aetiology of anxiety disorders and obsessive compulsive disorder (OCD) are currently based on a combination of vulnerability factors (genetic, early childhood adversity) as well as stressful exposure, e.g., occupational stress and traumatic experiences. Most probably, anxiety disorders are caused by an interaction of a specific neurobiological vulnerability and such environmental factors. The vulnerability may be based on genetic factors associated with neurobiological adaptation of the central nervous system. Neurobiological dysfunctions that have been found in anxiety and OCD patients include dysfunctions of serotonin, noradrenaline, dopamine, gamma-aminobutyric acid, cholecystokinin, glutamate, or endogenous opioid receptors or the hypothalamic-pituitary-adrenal (HPA) axis. The reader is referred to comprehensive reviews of the field (Charney and Bremner 1999; Connor and Davidson 1998; Gorman et al. 2000; Jetty et al. 2001; Leonardo and Hen 2006, 2008; Li et al. 2001; Nutt et al. 1998; Ressler and Mayberg 2007; Schneier et al. 2000; Stein 2000; van Ameringen et al. 2000) Also, a maladaptive physiological suffocation alarm system was postulated (Klein 1993; Preter and Klein 2008).

Treatment

Before drug treatment is initiated, the mechanisms underlying psychic and somatic anxiety should be explained to the patient. It is recommended to use brochures that explain the typical features of the patient's condition, treatment options, and adverse drug effects. Compliance with drug treatment can be improved when the advantages and disadvantages of the drugs are explained carefully to the patient, such as the delayed onset of effect or possible side effects like initial jitteriness associated with SSRI treatment.

A marked placebo effect, spontaneous remission or tendency of regression to the mean are well-known experiences in the treatment of anxiety disorders. It is not recommended to use treatments that fail to show superiority to placebo. Placebo effects are unpredictable in the individual patient and may fade out with time. Moreover, by using invalidated treatments, patients may be denied available effective alternative options. Considerable costs may arise for the general health system and for the society by prescription of treatments without controlled proof of efficacy.

Indication for treatment

Treatment is indicated in most patients who fulfill the ICD-10 or DSM-IV-TR criteria for an anxiety disorder or OCD. The treatment plan is based on the patient's preference, severity of illness, comorbidity, concomitant medical illnesses, complications like substance abuse or suicide risk, the history of previous treatments, cost issues and availability of types of treatment in a given area. Treatment options include drug treatment, psychological therapy and other interventions.

Duration of drug treatment

Mostly, anxiety disorders have a waxing and waning course. After remission, which may occur later in OCD and PTSD than in the other anxiety disorders, treatment should continue following a response for at least one year in order to reduce the risk of relapse, and only after all, or almost all, symptoms disappear. In general, few studies examine relapse prevention after a period of more than one year.

Dosing

Recommended dosages are given in Table VI. In randomized controlled trials, the SSRIs/SNRIs have a flat response curve, i.e. approximately 75% of patients respond to the initial (low) dose (with the exception of OCD). In some patients, such as the elderly, treatment should be started with half the recommended dose or less in order to minimize initial adverse drug events, such as nausea, dizziness and headache and a paradoxical increase in anxiety. In particular, patients with panic disorder may be sensitive to serotonergic stimulation and may easily discontinue treatment because of initial jitteriness and nervousness. For tricyclic antidepressants, it is recommended to initiate the drug at a low dose and increase dose every 3–5 days. The antidepressant dose should be increased to the highest recommended therapeutic level if the initial treatment with a low or medium dose fails. For obsessive-compulsive disorder, medium to high doses are recommended.

Although controlled data on maintenance treatment are scarce, it is recommended to use the same dose as in the acute phase ("what makes you better, keeps you better").

In order to increase compliance, it is preferred to take medications in a single dose, if pharmacokinetic data support once daily dosing, depending upon the patient's tolerance.

In elderly patients, lower doses are used, especially when using tricyclic antidepressants.

Benzodiazepine doses should be as low as possible, but as high as necessary.

In patients with hepatic impairment, a dosage adjustment or use of medications with primarily renal clearance (e.g., pregabalin) may be required.

Monitoring treatment efficacy

In order to monitor treatment efficacy, it may be useful to apply symptom rating scales such as the Panic and Agoraphobia Scale (PAS; (Bandelow 1999) for panic disorder, the Hamilton Anxiety Scale (HAM-A; Hamilton 1959) for generalized anxiety disorder, the Liebowitz Social Phobia Scale (LSAS; Liebowitz 1987) for social anxiety disorder, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al. 1989a) for obsessive-compulsive disorder, and the Clinician-Administered PTSD Scale (CAPS; Blake et al. 1995) for post-traumatic stress disorder. However, as these assessments are time-consuming, global improvement ratings such as the Clinical Global Impression (NIMH 1976) may suffice in busy practice settings. Alternatively, using disorders specific self-report measures may be less time-consuming.

Treatment resistance

A substantial number of patients with anxiety disorders do not fulfill response criteria after initial standard treatment. While no universally accepted criteria exist, a commonly used threshold for response is a $>50\%$ improvement in the total score of a commonly used rating scale (e.g., the HAMA), however, this definition is somehow arbitrary and not fully supported by clinical data (Bandelow 2006; Bandelow et al. 2006).

Before considering a patient to be treatment-refractory, the diagnosis should be reviewed, the patient should be assessed for compliance with therapy, the dosage should be confirmed as within the therapeutic range and the trial period should be adequate. Concurrent prescription drugs (or traditional medicines) may interfere with efficacy, e.g., metabolic enhancers or inhibitors. Poor therapeutic alliance and a number of psychosocial stress factors may also impair response, along with concomitant personality disorders, which may be associated with poor outcome. Depression and substance abuse have to be considered as complicating factors. Past treatment history of the patient should be used as guide to practice.

When initial treatment fails, the physician has to consider to change the dose or to switch to another medication. Controlled data on switching medications are lacking for the anxiety disorders. If the patient does not respond to treatment in an adequate dose after 4–6 weeks (8–12 weeks in obsessive-compulsive or post-traumatic stress disorder), medication should be changed. If partial response is seen after this period, there is still a chance that the patient will respond within the next 4–6 weeks of therapy. For elderly patients it may take longer to see a response.

In some patients unresponsive to medications, the addition of cognitive behavioural therapy was successful.

Although "switching studies" are lacking, many treatment-resistant patients are reported by experienced clinicians to respond when a different class of medication is tried (e.g., switching from SSRI/SNRIs to TCAs or *vice versa*). However, the issue of "switching" versus "augmenting" currently remains open.

Special recommendations for the different anxiety disorders are given below.

Non-pharmacological treatment

In order to be complete, the evidence for non-pharmacological treatment modalities is briefly summarised in this article. However, these guidelines deal with pharmacological treatments and do not represent an in-depth discussion of other modalities.

All patients with anxiety disorders require supportive interviews and attention to emotional states. "Psychoeducation" is essential and includes information about the aetiology and treatment of anxiety disorders, OCD, and PTSD.

Many patients may require specific psychological treatment interventions. The effect sizes obtained with psychological therapies for anxiety disorders are as high as the effect sizes achieved with drug treatment (Bandelow et al. 2007a). Psychological and pharmacological treatment modalities must be seen as partners, not alternatives, in the treatment of anxiety disorders. Exposure therapy (e.g., gradual exposure in vivo, "flooding") and response prevention were found to be very effective in specific phobia, agoraphobia, social phobia and OCD. In this treatment modality, patients are confronted "in vivo" with a feared situation (e.g., using public transport in agoraphobia). For symptoms which cannot be treated with exposure, such as spontaneous panic attacks, worrying or obsessive thoughts, various cognitive strategies have been proposed.

The effective treatment of anxiety disorders with cognitive-behaviour therapy has been demonstrated in many controlled studies, as was summarized in a meta-analysis of 108 studies (Norton and Price 2007). However, the number of studies comparing CBT to a placebo condition is limited for anxiety disorders, OCD and PTSD (Hofmann and Smits 2008). Some evaluations of the efficacy of

psychological treatments have not employed an optimal control treatment. Demonstrating the superiority to a wait list control is a first step to validate a new psychotherapeutic method, but not sufficient as efficacy proof, as the wait list condition may be associated with negative demoralizing effects. It only shows that the treatment is superior to "no treatment", but in order to show that a psychological therapy also has effects beyond non-specific factors such as attention, evidence is needed that it is more effective than a "psychological placebo" ("attention placebo"), i.e. a nondirectional, neutral discussion between the patient and the treatment provider, in which no specific psychotherapeutic techniques like "cognitive restructuring" are applied. For anxiety disorders, trials comparing CBT to a wait-list control group found significantly larger effect sizes than those comparing CBT to an attention placebo (Haby et al. 2006), and "psychological placebos" seem to have the same effect size as a pill placebo (Hofmann and Smits 2008).

It is difficult, but not impossible, to protect the blind in psychotherapy studies. A rater blind to the treatment condition may reduce expectancy biases on the investigator side, but not on the patient side.

Due to limited financial resources, evaluations of psychological therapies often do not have the optimal sample sizes, which limits their interpretability. Very often, when two or more different active psychological treatments or techniques were compared, the result was "no difference". In many cases, this may have been due to the fact that in these studies sample sizes were used that were far too small for non-inferiority trials. Recent non-inferiority drug trials used between 80 and 300 subjects per arm, and as the average effect sizes with psychological therapy are not higher than with drug treatment, the same sample size requirements apply for psychotherapy trials.

Only a few published studies provided data that were corrected for attrition (i.e., ITT analysis using last-observation-carried-forward method) (Hofmann and Smits 2008).

An advantage of psychological treatments is an apparent lack of side effects in the true sense of the word. However, techniques like exposure and response prevention have high rates of therapy refusal and attrition due to unpleasant feelings during sessions and related anticipatory anxiety. Overdependence on the therapist has also been observed. Like drug treatment, psychological therapy also may show insufficient efficacy. Also, relapses or even a deterioration of the symptoms is possible. Response may be delayed and occurs usually later than with drug treatment. Prolonged courses of treatment are often needed to maintain an initial treatment response. Demonstrating efficacy of psychotherapy in a trial conducted at an expert site does not guarantee that the same effect sizes are obtained in "real life" (Nutt and Sharpe 2008).

Cognitive behavioural therapy is reputed to maintain its treatment gains over time, which would be a distinct advantage over medications and would also justify its higher treatment costs. However, only a few studies could demonstrate the superiority of CBT over a control group (e.g., relaxation) at follow-up, while more studies failed to show a difference (see page 46).

The choice between medications and CBT is determined by a number of factors, particularly the patient's preference, treatment options at hand, adverse drug effects, onset of efficacy, comorbidity (e.g., with depression), economic considerations, time availability and commitment of the patient, accessibility of psychiatric and psychological treatment resources, and qualification and experience of the clinician. Unfortunately, in many regions of the world, the availability of CBT is often limited.

Psychodynamic therapy is frequently used in the treatment of patients with anxiety disorders. However, there is only one published report of a randomized trial in panic disorder showing the superiority of this approach to a control condition, while in generalized anxiety disorder, psychodynamic therapy was less effective than CBT (see below for references).

For most other psychological treatments, no sufficient support of efficacy exists.

Drug treatment: Available compounds

Several psychopharmacological agents are available for the treatment of anxiety disorders; these are briefly reviewed in the following section. These recommendations are based on clinical studies, which are presented in the section "Special treatment recommendations for the different anxiety disorders".

For details of the treatment with psychopharmacological drugs, the reader is referred to the specific literature.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are the first-line drugs for the treatment of anxiety disorders, OCD and PTSD. All available compounds have shown to be effective in one or more anxiety disorders, with the exception of specific phobia (see below for references).

Although treatment with SSRIs is usually well tolerated, restlessness, jitteriness, an increase in

anxiety symptoms, insomnia or headache in the first days or weeks of treatment may jeopardize compliance with treatment. Lowering the starting dose of SSRIs may reduce this overstimulation. Other side effects include headache, fatigue, dizziness, nausea, anorexia or weight gain. Sexual dysfunctions (decreased libido, impotence or ejaculatory disturbances) may be a problem in long-term treatment, and discontinuation syndromes have been observed, especially with paroxetine (Bandelow et al. 2002a; Price et al. 1996; Stahl et al. 1997).

The anxiolytic effect may start with a delay of 2–4 weeks (in some cases up to 6 or 8 weeks). To avoid overstimulation and insomnia, doses might be given in the morning or at mid-day, except in patients reporting daytime sedation.

Selective serotonin norepinephrine reuptake inhibitors (SNRIs)

The efficacy of the selective serotonin norepinephrine reuptake-inhibitors venlafaxine and duloxetine in certain anxiety disorders has been shown in several controlled studies (see below for references). At the beginning of treatment, side effects like nausea, restlessness, insomnia or headache may pose a threat to compliance with treatment. Also, sexual dysfunctions, discontinuation syndromes and other adverse events may be reported. A modest, sustained increase in blood pressure can occur with venlafaxine and duloxetine.The antianxiety effect of SNRIs may have a latency of 2–4 weeks, and in some cases even later.

Tricyclic antidepressants (TCAs)

The efficacy of tricyclic antidepressants in anxiety disorders and OCD is well proven, mainly for imipramine and clomipramine (see below for references). However, TCAs have not been investigated systematically in social anxiety disorder.

Especially at the beginning of treatment, compliance may be reduced by adverse effects such as initially increased anxiety, dry mouth, amblyopia, postural hypotension, tachycardia, sedation, sexual dysfunctions, impaired psychomotor function/car driving safety, and others. Weight gain may be a problem in long-term treatment. Stopping TCAs abruptly can also cause a discontinuation syndrome, and pharmacokinetic interactions can limit their use in patients taking concomitant medication. Elderly patients should be monitored for cardiovascular side effects. TCAs should be avoided in patients considered at risk of suicide, due to their potential cardiac and CNS toxicity after overdose (Nutt 2005). In general, the frequency of adverse events is higher for TCAs than for newer antidepressants, such as the SSRIs or SNRIs. Thus, the latter drugs should be tried first before TCAs are used.

The dosage should be titrated up slowly until dosage levels as high as in the treatment of depression are reached. Patients should be informed that the onset of the anxiolytic effect of the drug may have a latency of 2–4 weeks (in some cases up to 6 weeks, and generally longer in OCD). During the first 2 weeks, side effects may be stronger. Also, during the first days of treatment, jitteriness or increase in anxiety symptoms may occur.

Calcium channel modulator pregabalin

Pregabalin was found to be effective in a number of studies in GAD and in a few trials in SAD. The anxiolytic effects of the drug are attributed to its potent binding to the α_2-δ-subunit protein of voltage-gated calcium channels in central nervous system tissues; binding at this site seems to underlie its anxiolytic, analgesic, and antiepileptic effects. Such binding reduces calcium influx at nerve terminals and modulates the release of neurotransmitters – including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide – from pathologically excited neurons. Pregabalin does not exacerbate GABA-mediated responses, nor does it affect GABA reuptake or GABA transaminase inhibition. It does not appear to alter rat brain GABA concentration, augment $GABA_A$ responses in cultured neurons, or exert acute effects on GABA uptake or degradation. However, it has been shown that prolonged exposure to pregabalin increases both the density of GABA transporter protein and the speed of functional GABA transport in cultured neurons (Bandelow et al. 2007c).

The main side effects include dizziness, sedation, dry mouth, amblyopia, impaired coordination, and impaired psychomotor and cognitive function. In preclinical and clinical studies, no addiction potential has been observed.

Reversible inhibitor of monoamine oxidase A (RIMA) moclobemide

The results with the reversible inhibitor of monoamine oxidase A (RIMA) moclobemide are inconsistent. Although the efficacy of moclobemide in social phobia has been shown in two placebo-controlled studies, another two studies failed to detect a difference to placebo and a fifth study showed only marginal effects (see below for references). In panic disorder, moclobemide failed in a double-blind study, but was equally effective in comparator trials (see below for references).

To avoid overstimulation and insomnia, doses should be given in the morning and mid-day.

Irreversible monoamine oxidase inhibitors (MAOIs)

The efficacy of the irreversible MAOI phenelzine in panic disorder, SAD and PTSD has been shown in some controlled studies (see below for references). Because of the possibility of severe side effects and interactions with other drugs or food components, the MAO inhibitors phenelzine and tranylcypromine are not considered first-line drugs and are used mostly by experienced psychiatrists when other treatment modalities have been unsuccessful or have not been tolerated. However, in these cases, they may be very useful. To avoid overstimulation and insomnia, doses should be given in the morning and mid-day. MAOIs should be used only after giving the patient proper explanation on the dietary restrictions and interactions with other medications.

Benzodiazepines

The efficacy of benzodiazepines in anxiety disorders has been shown in many controlled clinical studies (see below for references). The anxiolytic effect starts within 30–60 minutes after oral or parenteral application. In contrast to antidepressants, they do not lead to initially increased nervousness. In general, they have a good record of safety. Due to CNS depression, benzodiazepine treatment may be associated with sedation, dizziness, prolonged reaction time and other side effects. Cognitive functions and driving skills may be affected. These effects that are aggravated by concurrent alcohol intake. After long-term treatment with benzodiazepines (e.g., over 2–8 months), dependency may occur in a substantial number of patients (Bradwejn 1993; Livingston 1994; Nelson and Chouinard 1999; Rickels et al. 1990; Schweizer et al. 1990b; Shader and Greenblatt 1993; Smith and Landry 1990), especially in predisposed patients (Schweizer et al. 1998). Withdrawal reactions have their peak severity at 2 days for short half-life and 4–7 days for long half-life benzodiazepines (Rickels et al. 1990). It is claimed that prolonged withdrawal reactions may occasionally occur; however, these are not distinguishable from the symptoms patients present before their first use of benzodiazepines. Tolerance to anxiolytic or other effects seems to be rare in long-term controlled trials (Nagy et al. 1989; Pollack et al. 1993; Rickels 1982; Worthington et al. 1998).

Treatments with benzodiazepines are indisputably safe and effective for short-term use. However, maintenance treatment requires a careful weighing of risks and benefits. Patients for whom other treatment modalities were not effective or were not tolerated due to side effects, a long-term treatment with benzodiazepines may be justified. However, patients with a history of benzodiazepine, alcohol or other psychoactive substance abuse or dependence should generally be excluded from treatment, or be closely monitored in specialized care settings. Cognitive-behavioural interventions may facilitate benzodiazepine discontinuation (Otto et al. 1993; Spiegel 1999).

Benzodiazepines may also be used in combination with serotonergic medications during the first weeks before the onset of mood-elevating effect to speed onset of efficacy or to suppress the increased anxiety sometimes seen when serotonergic therapy is initiated (Goddard et al. 2001). In depressed patients, drop-out rates were lower when benzodiazepines were added to antidepressant treatment (Furukawa et al. 2002).

In general, benzodiazepines should be used with a regular dosing regimen and not on a p.r.n. basis. Only in the treatment of short-term distress (e.g., air travel or dental phobia), p.r.n. use may be justified.

A large number of benzodiazepines have received approval for the treatment of "anxiety states" or "anxiety disorders" prior to the DSM-III nosology based on specified diagnostic criteria. However, in the present guideline, recommendations of benzodiazepines are restricted to the ones that have been studied in patients with DSM- or ICD-defined diagnoses.

When treating comorbid anxiety disorders, one should be aware that benzodiazepines were not found to be effective in comorbid conditions, such as depression or OCD.

5-HT_{1A}-agonist buspirone

The 5-HT_{1A}-agonist (azapirone) buspirone may be effective for symptoms of generalized anxiety disorder, as shown in some controlled studies (see below for references). In other anxiety disorders, studies were mostly negative. Side effects include headache, dizziness, lightheadedness, restlessness, fatigue, paresthesias and others.

Antihistamines

The antihistamine hydroxyzine was effective in generalized anxiety disorder in a number of DBPC studies (see below for references). Because of sedating effects, the antihistamine should only be used when treatment with other medications has not been successful or was not tolerated. Experience with long-term treatment is lacking. There is no antidepressant effect, nor effects in panic or social

anxiety disorder, PTSD or OCD. Side effects include sedation, anticholinergic effects at high doses, blurred vision, confusion, delirium and others.

Atypical antipsychotics

In the 1970s and 1980s, anxiety disorders were frequently treated with typical high or low potency antipsychotics such as haloperidol, fluspirilene, flupentixol, sulpiride, chlorprothixene, melperone and others at lower doses than are used in the treatment of schizophrenia. However, studies carried out with antipsychotics in the 1970s and 1980s in patients suffering from "anxiety neuroses" had some methodological flaws. Moreover, there were concerns regarding tardive side effects after year-long treatment, which is often required in the treatment of anxiety disorders. Therefore, the use of typical antipsychotics was abandoned, as alternative medications emerged for the treatment of anxiety disorders. However, according to new studies, the atypical antipsychotic quetiapine was reported to be effective as a monotherapy for generalized anxiety disorder and may be an option for the treatment of anxiety disorders in the future.

In a number of studies, atypical antipsychotics have been used as add-on treatment for non-responsive cases of anxiety disorders, OCD and PTSD.

Side effects of atypical antipsychotics include sedation, orthostatic hypotension, sexual dysfunctions, metabolic syndrome, extrapyramidal effects and others.

Anticonvulsants

Anticonvulsants, including carbamazepine, valproate, lamotrigine, topiramate and gabapentin had shown efficacy in preliminary studies and deserve further research. However, they are not used in routine treatment.

Beta-adrenergic blockers

Because beta-blockers may influence autonomic anxiety symptoms such as palpitations, tremor etc., they have been used in the treatment of anxiety disorders. However, available double-blind studies were not able to show efficacy of beta-blockers in any anxiety disorder (see below for references). Moreover, patients with anxiety disorders frequently suffer from low blood pressure or postural hypotension, and these conditions may be intensified by beta-blockers.

Propranolol has been shown to improve vegetative anxiety symptoms such as tremor in musicians with performance anxiety, but this condition differs from generalized social anxiety disorder.

Homeopathic and herbal preparations

In some countries, herbal preparations such as St. John's wort or Valerian are used in the treatment of anxiety disorders. Sufficient support of efficacy is not available for these preparations; on the contrary, effect-size analyses of available trials indicate a worsening of symptoms (Hidalgo et al. 2007). Thus, there is no proof of efficacy for the treatment of anxiety disorders, OCD or PTSD with homeopathic preparations.

Initial improvement with these compounds may be due to placebo effects, spontaneous remission or tendency of regression to the mean. Herbal and homeopathic preparations are sometimes used in the hope that advantage can be taken of these unspecific effects and adverse events can be minimized. However, placebo effects are usually not long-lasting, and a re-occurence or deterioration of the symptomatology may result in loss of confidence in the physician. Also, these preparations have not undergone a thorough safety evaluation (for example, St. John's wort may cause skin reactions, and *Kava kava* extracts have been taken from the market due to possible hepatotoxicity). Case reports indicate that they may interact with the metabolism of prescribed anxiolytics and other medications. The prescription of these compounds may result in considerable costs for the health system.

Advantages and disadvantages of antianxiety drugs

None of the available drug treatments can be considered as ideal for every patient. In Table V, risks and benefits of the available compounds are reviewed. The treatment option should be chosen individually for each patient. Also, medications costs have to be taken into account weighing the advantages and disadvantages against each other.

Special treatment recommendations for the different anxiety disorders

In Table VI, treatment recommendations for the drug treatment of anxiety disorders and OCD are shown.

These recommendations are based on randomized, double-blind clinical studies published in peer-reviewed journals. Not all of the recommended drugs are licensed for these indications in every country.

Table V. Advantages and Disadvantages of Antianxiety Drugs.

Substance	Advantages	Disadvantages
SSRIs	No dependency Sufficient evidence from clinical studies for all anxiety disorders Relatively safe in overdose	Latency of effect 2–6 weeks, initial jitteriness, nausea, restlessness, sexual dysfunctions and other side effects. Some risk of discontinuation syndromes.
SNRIs	No dependency Sufficient evidence from clinical studies Relatively safe in overdose	Latency of effect 2–6 weeks, nausea, possible increase in blood pressure and other side effects. Some risk of discontinuation syndromes.
Pregabalin	No dependency Sufficient evidence from clinical studies Rapid onset of effect	Dizziness, sedation and other side effects
Quetiapine	No dependency Preliminary evidence from clinical studies Rapid onset of effect	Somnolence, weight gain and other side effects
TCAs	No dependency Sufficient evidence from clinical studies (exception: SAD, PTSD)	Latency of effect 2–6 weeks, anticholinergic effects, cardiac side effects, weight gain and other side effects, may be lethal in overdose
Benzodiazepines	Rapid onset of action Sufficient evidence from clinical studies Relatively safe in overdose	Dependency possible; sedation, slow reaction time and other side effects. Paradoxical reactions in elderly patients.
Moclobemide	No dependency Benign side effect; relatively safe in overdose	Latency of effect 2–6 weeks, inconsistent study results in SAD, no efficacy proofs for other anxiety disorders
MAOIs	No dependency	Few supporting studies in PD and SAD; latency of effect 2–6 weeks; potentially dangerous side effects and interactions
Buspirone	No dependency Relatively safe in overdose	Latency of effect 2–6 weeks; efficacy proofs only for symptoms of GAD; lightheadedness, nausea and other side effects
Hydroxyzine	No dependency	Efficacy proofs only for GAD; sedation and other side effects; no experience with long-term treatment

TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, selective serotonin noradrenaline reuptake inhibitors; GAD, generalized anxiety disorder; PD, panic disorder; SAD, social anxiety disorder.

Panic disorder and agoraphobia

In acute panic attacks, reassurance of patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines may be needed (e.g., melting tablets).

Selective serotonin reuptake inhibitors (SSRIs). The efficacy of the SSRIs in panic disorder has been proven in many controlled studies, and they are considered to be the first-line drugs for this disorder.

- *Citalopram* was effective in a placebo- and comparator-controlled trial (Wade et al. 1997) and one comparison with fluoxetine (Amore et al. 1999b). In a relapse prevention study over 52 weeks, it was superior to placebo and as effective as the TCA clomipramine (Lepola et al. 1998). In a long-term study that included 24 weeks double-blind treatment and an open extension of another 26 weeks, citalopram was as effective as fluoxetine (Amore et al. 1999b) (A).
- *Escitalopram* was effective in a citalopram- and placebo-controlled trial (Bandelow et al. 2007b; Stahl et al. 2003). Escitalopram is the *S*-enantiomer of the racemate citalopram; therefore the clinical studies with citalopram may also be relevant for escitalopram (A).
- *Fluvoxamine* showed efficacy in a number of DBPC studies (Asnis et al. 2001; Black et al. 1993; de Beurs et al. 1995; den Boer and Westenberg 1990; Hoehn-Saric et al. 1993; Pols et al. 1993). In one study, fluvoxamine and the comparator imipramine were both more effective than placebo and equally effective (Bakish et al. 1996). One small study did not show superiority to placebo on the main efficacy measure, but did on some other instruments (Sandmann et al. 1998). Another study did not show efficacy for fluvoxamine, but demonstrated a strong effect for imipramine in comparison to placebo (Nair et al. 1996) (A).
- *Fluoxetine* was effective in DBPC (Michelson et al. 1998, 2001) and comparator-controlled trials (Amore et al. 1999b; Bystritsky et al. 1994). In a 26-week long-term study, it was as effective as imipramine (Amore et al. 1999a). In a 52-week long-term study, it was as effective as the RIMA moclobemide (Tiller et al. 1999) (A).

Table VI. Recommendations for the Drug Treatment of Anxiety Disorders And OCD. Categories of Evidence are Only Based on Efficacy without Regard to Other Properties (e.g., Side Effects). Abbreviations: See Text. Category of Evidence: see Table II.

Diagnosis	Treatment	Examples	Category of evidence	Recommendation grade	Recommended daily dose for adults
Panic disorder and agoraphobia					
	SSRIs, e.g.,	Citalopram	A	1	20–60 mg
		Escitalopram	A	1	10–20 mg
		Fluoxetine	A	1	20–40 mg
		Fluvoxamine	A	1	100–300 mg
		Paroxetine	A	1	20–60 mg
		Sertraline	A	1	50–150 mg
	SNRI	Venlafaxine	A	1	75–225 mg
	TCA, e.g.,	Clomipramine	A	2	75–250 mg
		Imipramine	A	2	75–250 mg
	Benzodiazepines, e.g.,	Alprazolam	A	2	1.5–8 mg
		Clonazepam	A	2	1–4 mg
		Diazepam	A	2	5–20 mg
		Lorazepam	A	2	2–8 mg
	MAOI	Phenelzine	B	3	45–90 mg
Generalized anxiety disorder					
	SSRIs	Escitalopram	A	1	10–20 mg
		Paroxetine	A	1	20–50 mg
		Sertraline	A	1	50–150 mg
	SNRIs	Venlafaxine	A	1	75–225 mg
		Duloxetine	A	1	60–120 mg
	TCA	Imipramine	A	2	75–200 mg
	Calcium channel modulator	Pregabalin	A	1	150–600 mg
	Atypical antipsychotic	Quetiapine	A	1	50–300 mg
	Benzodiazepines, e.g.,	Diazepam	A	2	5–15 mg
		Lorazepam	A	2	2–8 mg
	Antihistamine	Hydroxyzine	A	2	37.5–75 mg
	Tricyclic anxiolytic	Opipramol	B	3	50–150 mg
	Azapirone	Buspirone	D	5	15–60 mg
Social anxiety disorder					
	SSRIs	Escitalopram	A	1	10–20 mg
		Paroxetine	A	1	20–50 mg
		Sertraline	A	1	50–150 mg
		Fluvoxamine	A	1	100–300 mg
		Citalopram	B	3	20-40 mg
		Fluoxetine	D	5	20–40 mg
	SNRI	Venlafaxine	A	1	75–225 mg
	MAOI	Phenelzine	A	2	45–90 mg
	Benzodiazepines, e.g.,	Clonazepam	B	3	1.5–8 mg
	Anticonvulsant	Gabapentin	B	3	600–3,600 mg
	RIMA	Moclobemide	D	5	300–600 mg
Obsessive-compulsive disorder					
	SSRIs, e.g.,	Escitalopram	A	1	10–20 mg
		Fluoxetine	A	1	40–60 mg
		Fluvoxamine	A	1	100–300 mg
		Paroxetine	A	1	40–60 mg
		Sertraline	A	1	50–200 mg
		Citalopram	B	3	20–60 mg
	TCA	Clomipramine	A	2	75–300 mg
	NASSA	Mirtazapine	B	3	30–60mg
	MAOI	Phenelzine	D	5	45–90 mg
Post-traumatic stress disorder					
	SSRIs, e.g.,	Fluoxetine	A	1	20–40 mg
		Sertraline	A	1	50–100 mg
		Paroxetine	A	1	20–40 mg
	SNRI	Venlafaxine	A	1	75–300 mg
	TCAs, e.g.,	Amitriptyline	B	3	75–200 mg
		Imipramine	B	3	75–200 mg
	NaSSA	Mirtazapine	B	3	30–60 mg
	Atypical Antipsychotic	Risperidone	B	3	0.5–6 mg

Table VI (*Continued*)

Diagnosis	Treatment	Examples	Category of evidence	Recommendation grade	Recommended daily dose for adults
	Atypical Antipsychotic	Olanzapine (adjunctive)	B	3	2.5–20 mg
	Anticonvulsant	Lamotrigine	B	3	25–500 mg
	α1-Antagonist	Prazosin (only for nightmares)	B	3	1–10 mg
	MAOI	Phenelzine	D	5	45–90 mg

- *Paroxetine* showed efficacy in DBPC (Ballenger et al. 1998; Oehrberg et al. 1995; Pollack and Doyle 2003; Sheehan et al. 2005) and comparator-controlled studies (Bakker et al. 1999; Bandelow et al. 2004; Lecrubier et al. 1997; Oehrberg et al. 1995; Pollack et al. 2007b; Wedekind et al. submitted). In a relapse prevention trial over 36 weeks, it was as effective as the TCA clomipramine (Lecrubier and Judge 1997) (A).
- *Sertraline* was also effective in DBPC studies (Londborg et al. 1998; Pohl et al. 1998; Pollack et al. 1998) and one non-inferiority comparator trial (Bandelow et al. 2004). In a relapse prevention study over 26 weeks, which followed open treatment over 1 year, sertraline was superior to placebo (Rapaport et al. 2001). In another relapse prevention study, responders in a DBPC study of 8 weeks were again randomized to sertraline or placebo. Sertraline outperformed placebo on most measures except the primary efficacy measure, relapse rate (Kamijima et al. 2005). In a long-term study over 26 weeks, sertraline was superior to placebo and as effective as imipramine in patients with panic disorder and comorbid depression (Lepola et al. 2003) (A).

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

The efficacy of the antidepressant venlafaxine, a selective serotonin norepinephrine reuptake-inhibitor, was demonstrated in DBPC studies (Bradwejn et al. 2005; Pollack et al. 1996). In the latter study, venlafaxine was not associated with a greater proportion of patients free from full-symptom panic attacks, but was associated with lower mean panic attack frequency and a higher proportion free from limited-symptom panic attacks, higher response and remission rates, and improvements in anticipatory anxiety, fear and avoidance. In two studies, venlafaxine was more effective than placebo and was as effective as the comparator drug paroxetine (Pollack et al. 2007a,b). In a relapse prevention study, 12 weeks of open treatment with venlafaxine were followed by 26 weeks of DBPC treatment (Ferguson et al. 2007). Venlafaxine was more effective than placebo in preventing relapses (A).

Tricyclic antidepressants (TCAs). Treatment with TCAs has been shown to improve panic disorder. This was shown for imipramine and clomipramine.

- *Imipramine* was effective in DBPC (Klein 1964; Zitrin et al. 1980, 1983) and comparator-controlled studies (CNCPS 1992; Nair et al. 1996; Sheehan et al. 1990; Uhlenhuth et al. 1989). In a relapse prevention study (8 weeks acute study, followed by up to 35 weeks relapse prevention), it was superior to placebo and as effective as alprazolam (Curtis et al. 1993). In another relapse prevention study, it was as effective as alprazolam in an 8-week acute DBPC study, and less effective than alprazolam in a 26-week DBPC extension (Rickels and Schweizer 1998). In a 26-week long-term study, it was as effective as fluoxetine (Amore et al. 1999a) (A).
- *Clomipramine* also showed efficacy in DBPC (Bandelow et al. 2000; Johnston et al. 1988) and comparator-controlled studies (Cassano et al. 1988; Fahy et al. 1992; Lecrubier et al. 1997; Modigh et al. 1992; Wade et al. 1997). In a relapse prevention trial over 36 weeks, it was as effective as the SSRI paroxetine (Lecrubier and Judge 1997) (A).
- *Lofepramine* was also effective in a DBPC with clomipramine as an active comparator (Fahy et al. 1992) (B).

In general, the frequency of adverse events is higher for TCAs than for newer antidepressants, such as the SSRIs (Amore et al. 1999a; Bakish et al. 1996; Bakker et al. 1999; Bystritsky et al. 1994; Lecrubier and Judge 1997; Lepola et al. 1998; Wade et al. 1997). Thus, the latter drugs should be tried first before TCAs are used.

Benzodiazepines. The efficacy of benzodiazepines in panic disorder has been shown in some controlled clinical studies.

- *Alprazolam* was superior to placebo and as effective as comparator drugs in a number of

studies (Andersch et al. 1991; Ballenger et al. 1988; CNCPS 1992; Lydiard et al. 1992; Noyes et al. 1996; Uhlenhuth et al. 1989). In a relapse prevention study (8 weeks acute study, followed by up to 35 weeks relapse prevention), it was superior to placebo and as effective as imipramine (Curtis et al. 1993). In another relapse prevention study, it was as effective as imipramine in an 8-week acute DBPC study, and more effective than imipramine in a 26-week DBPC extension (Rickels and Schweizer 1998) (A).

- *Clonazepam* was effective in DBPC studies (Beauclair et al. 1994; Dyukova et al. 1992; Moroz and Rosenbaum 1999; Rosenbaum et al. 1997) and one placebo- and comparator-controlled trial (Tesar et al. 1991) (A).
- *Diazepam* was superior to placebo and as effective as alprazolam in two studies (Dunner et al. 1986; Noyes et al. 1996) (A).
- *Lorazepam* was as effective as alprazolam in two studies, and both drugs were superior to placebo (Charney and Woods 1989; Schweizer et al. 1990a) (A).

In clinical practice, benzodiazepines are often combined with SSRIs, SNRIs or TCAs. In a study examining this combination, patients were treated with paroxetine and clonazepam or with paroxetine and placebo. Combined treatment with paroxetine and clonazepam resulted in more rapid response than with the SSRI alone, but there was no differential benefit beyond the initial few weeks of therapy (Pollack et al. 2003b). Similar placebo-controlled studies involved a combination of imipramine and alprazolam (Woods et al. 1992) and sertraline and clonazepam (Goddard et al. 2001), and both showed a faster response to these combinations than to imipramine and sertraline plus placebo, respectively.

Monoamine oxidase inhibitors (MAOI). Despite the wide-spread use of *phenelzine* in panic disorder, evidence is only based on one study (Sheehan et al. 1980). In this study, phenelzine was superior to placebo and equal to imipramine or even superior on some measures (B).

Other medications. Some available drugs have shown preliminary evidence or mixed results. Some practitioners use these drugs "off-label" in patients with non-response to standard treatments.

- The results with the reversible inhibitor of monoamine oxidase (RIMA) *moclobemide* were inconsistent. Moclobemide was as effective as fluoxetine (Tiller et al. 1999) or clomipramine (Krüger and Dahl 1999). However, it was not superior to placebo in a double-blind study (Loerch et al. 1999). In another study, superiority to placebo could only be established for the more severely ill patients, but not for the whole group (Uhlenhuth et al. 2002). In a 52-week long-term study, it was as effective as fluoxetine (Tiller et al. 1999). Thus, the drug may be a treatment option for otherwise unresponsive patients. It is not available in the US, but is in Canada and many other countries. Side effects include restlessness, insomnia, dry mouth, and headache. To avoid overstimulation and insomnia, doses should be given in the morning and mid-day (D).
- The efficacy of the norepinephrine (noradrenaline) reuptake inhibitor (NaRI) *reboxetine* was shown in a DBPC study (Versiani et al. 2002). In single-blind studies, the drug was as effective as fluvoxamine (Seedat et al. 2003), but less effective than paroxetine (Bertani et al. 2004) (D). The drug is not available in the US, but again is available in many other countries.
- In a small double-blind comparison of *mirtazapine* and fluvoxamine, no differences were found between the two drugs (Ribeiro et al. 2001) (C1).
- The anticonvulsant *valproate* (valproic acid) was effective in one very small DBPC cross-over study (Lum et al. 1990). Because of the small sample size, evidence can only be seen as preliminary (C1).
- The intracellular second-messenger precursor *inositol* showed superiority to placebo in a small DBPC study (Benjamin et al. 1995) and was as effective as the SSRI fluvoxamine (Palatnik et al. 2001). Because of the small sample size, evidence can only be seen as preliminary (C1).
- In a DBPC study, the anticonvulsant *gabapentin* was only superior to placebo in more severely ill panic patients (Pande et al. 2000) (E).
- In panic disorder, buspirone was not superior to placebo (Sheehan et al. 1990, 1993) and less effective than imipramine (Sheehan et al. 1990), clorazepate (Schweizer and Rickels 1988) and alprazolam (Sheehan et al. 1993) (E).
- *Bupropion*, a norepinephrine-dopamine reuptake inhibitor, was not effective in a small controlled study (Sheehan et al. 1983) (E).
- Because beta-blockers may influence autonomic anxiety symptoms such as palpitations, tremor, etc., they have been used in the treatment of panic disorder. However, the

beta-blocker *propranolol* was not superior to placebo (Munjack et al. 1989) and less effective than comparator drugs (Munjack et al. 1989; Noyes et al. 1984). In another DBPC study with small sample size, propranolol was not different from alprazolam, although alprazolam showed a more rapid onset of efficacy (Ravaris et al. 1991) (E).

Although herbal preparations such as St. John's Wort or Valerian extracts are often taken by panic patients (Bandelow et al. 1995), there are no controlled studies showing efficacy for any herbal treatment.

Open trials with other compounds are listed in Table VII.

Long-term treatment. Typically, panic disorder has a waxing and waning course. After remission, treatment should continue for at least several months in order to prevent relapses. A number of studies have investigated the long-term value of drug treatments. Some of these trials are *long-term studies* comparing a drug and placebo for a longer period (i.e. 26–60 weeks). The other type of trials are *relapse prevention studies*, in which patients usually receive open label treatment with the study drug for a shorter period, after which responders are randomized to receive ongoing active drug treatment or placebo. In summary, SSRIs, the SNRI venlafaxine, tricyclic antidepressants, benzodiazepines and moclobemide showed long-term efficacy in these studies (see above for references).

Data on how long maintenance treatment should be continued are scarce. In one study, patients who had 18 months of maintenance treatment with imipramine had fewer relapses after discontinuation than patients who were discontinued after only 6 months of treatment. The results support the hypothesis that successful imipramine maintenance treatment of patients with panic and agoraphobia can have protective effects against relapse, at least in the first 6 months after the maintenance treatment period (Mavissakalian and Perel 1992a).

Expert consensus conferences generally recommend a duration of pharmacotherapy of at least 12–24 months (Table I).

Regarding SSRIs, the same doses are usually prescribed in the maintenance treatment of panic disorder as in the acute treatment phase. To our knowledge, there are no studies examining reduced doses of SSRIs in maintenance treatment. In an open study with the TCA imipramine, patients stabilized on imipramine who received further treatment with half their previous dose of imipramine did not show relapse or sustained worsening (Mavissakalian and Perel 1992b).

Comparisons of antipanic drugs. In studies comparing the efficacy of TCAs and SSRIs, no differences in terms of efficacy could be found between the two classes of drugs (Amore et al. 1999a; Bakish et al. 1996; Bakker et al. 1999; Bystritsky et al. 1994; Cavaljuga et al. 2003; Lecrubier and Judge 1997; Wade et al. 1997), with the exception of maprotiline, which had no effect in contrast to fluvoxamine (den

Table VII. Panic Disorder: Open Trials and Case Reports

Disorder	Drugs	Authors	Efficacy
Panic disorder			
	NaSSA mirtazapine	Carpenter et al. 1999	Yes (C1)
	SNRI milnacipran	Blaya et al. 2007	Yes (C1)
	5-HT_3 antagonist ondansetron	Schneier et al. 1996	Yes (C1)
	norepinephrine-dopamine reuptake inhibitor bupropion	Simon et al. 2003	Yes, but not effective in DBPC studies (E)
	anticonvulsant valproate	Primeau et al. 1990; Keck et al. 1993; Woodman and Noyes 1994	Yes (C1)
	Selective GABA reuptake inhibitor anticonvulsant tiagabine	Zwanzger et al. 2001b	Yes (C1)
	Irreversible inhibitor of GABA transaminase vigabatrin	Zwanzger et al. 2001a	Yes (C1)
Panic disorder, treatment-resistant			
	Olanzapine	Hollifield et al. 2005	Yes (C1)
	Addition of fluoxetine to a TCA/addition of TCA to fluoxetine	Tiffon et al. 1994	Yes (C1)
	Addition of olanzapine to an SSRI	Chao 2004; Etxebeste et al. 2000; Khaldi et al. 2003; Sepede et al. 2006	Yes (C1)
	Addition of lithium to clomipramine	Cournoyer 1986	Yes (C2)
	Valproate and clonazepam	Ontiveros and Fontaine 1992	Yes (C2)

Boer and Westenberg 1988). In most of these studies, the SSRIs were better tolerated than the TCAs, although one analysis did not find a difference in tolerability between SSRIs and imipramine (Otto et al. 2001). Also, in patients with comorbid panic disorder and major depressive disorder, both sertraline and imipramine were equally effective, but sertraline showed significantly greater tolerability and compliance than imipramine (Lepola et al. 2003).

Some comparisons among the SSRIs did not reveal differences with regard to efficacy (Bandelow et al. 2004; Perna et al. 2001), while escitalopram showed evidence of superiority over citalopram on some outcome measures (Bandelow et al. 2007b).

There are no direct comparisons between SSRIs and benzodiazepines in the treatment of panic disorder. According to a meta-analysis, the effect sizes for the SSRIs were higher than for the benzodiazepine alprazolam (Boyer,1995).

In a number of studies, alprazolam was compared with the tricyclic antidepressant imipramine (Andersch et al. 1991; Charney et al. 1986; CNCPS 1992; Lepola et al. 1990; Rizley et al. 1986; Taylor et al. 1990; Uhlenhuth et al. 1989). No differences could be found between the two drugs in terms of global improvement.

Treatment-resistant panic disorder. Only a few studies with treatment-resistant panic patients are available. In the only existing preliminary DBPC study, it was demonstrated that *pindolol* has a modest augmenting effect on fluoxetine in patients with treatment-resistant panic disorder (Hirschmann et al. 2000). Open studies are listed in Table VII.

When initial treatments have failed and after the doses were increased to the maximum tolerated doses, patients should first be switched to other first-line standard treatments, e.g., from an SSRI to an SNRI or *vice versa*. As the SSRIs are chemically different compounds, also a switch from one SSRI to another is also justified (Bandelow and Rüther 2004). As the next step, second-line drugs should be tried, e.g., TCAs. Then, drugs may be used that were effective, but not in all trials, e.g., moclobemide. Last, drugs or drug combinations that were effective in open studies and case reports may be an option.

In studies without control condition, patients having residual symptoms despite being on an adequate dose of medication showed improvement after the introduction of CBT (Heldt et al. 2003; Pollack et al. 1994). Conversely, SSRIs or clomipramine can improve patients who responded insufficiently to CBT, according to placebo-controlled studies (Hoffart et al. 1993; Kampman et al. 2002).

Non-pharmacological treatment. Among non-pharmacological treatments, cognitive-behaviour therapy has been investigated thoroughly. Exposure therapy is used to treat agoraphobia, and cognitive therapy including interoceptive exposure was developed for treating spontaneous panic attacks (Barlow 1997; Marks et al. 1993). As this review is focused on drug therapy, the reader is referred to the relevant literature for a detailed description of cognitive-behaviour therapy.

Cognitive-behavioural techniques were superior to waiting list control condition in a number of studies in panic disorder and/or agoraphobia (Barlow et al. 1989; Gould and Clum 1995; Klosko et al. 1990; Lidren et al. 1994; Margraf et al. 1993; Swinson et al. 1995; Telch et al. 1993, 1995; Williams and Falbo 1996), with one exception (Gould et al. 1993).

Superiority to a pill placebo or a psychological placebo was demonstrated in some studies (Barlow et al. 2000; Beck et al. 1992; Carlbring et al. 2006; Klosko et al. 1990; Marks et al. 1983, 1993; Mavissakalian and Michelson 1983; Murphy et al. 1998), while others found no difference to the control condition (Bakker et al. 1999; Black et al. 1993; Mavissakalian and Michelson 1986; Michelson et al. 1988; Shear et al. 1994).

Comparisons of psychological and pharmacological interventions and their combination. In direct comparisons of cognitive behaviour or exposure therapy with psychopharmacological treatment, drugs were superior in three studies (Bakker et al. 1999; Black et al. 1993; Mavissakalian and Michelson 1986). No differences were found in five studies (Clark et al. 1994; Klosko et al. 1990; Marks et al. 1983; Sharp et al. 1997; Telch et al. 1985) and an open study (Dannon et al. 2004), while one study showed inconsistent results (Marks et al. 1993).

As the aetiology of the anxiety disorder is multifactorial, the combination of drug treatment and cognitive behaviour therapy seems rational. The combination was superior to psychological therapy alone in the vast majority of studies (Barlow et al. 2000; Cottraux et al. 1995; de Beurs et al. 1995; Gladsjo et al. 2001; Marks et al. 1993; Mavissakalian and Michelson 1986; Oehrberg et al. 1995; Stein et al. 2000; Telch et al. 1985; Zitrin et al. 1980, 1983), whereas only two studies showed no difference between combined treatment and psychological therapy (Marks et al. 1983; Sharp et al. 1997). Despite statements implying the opposite, there is no methodologically sound study showing that drugs lessen the gains with CBT. The combination of CBT or psychodynamic treatment with a drug was superior to drug therapy alone in two studies without

control group for the psychotherapy condition (Mavissakalian et al. 1983; Wiborg and Dahl 1996), whereas three studies failed to show a difference between the combination and CBT alone (Barlow et al. 2000; Marks et al. 1983; Sharp et al. 1997).

A number of meta-analyses have led to contradictory results regarding the efficacy of the psychological and pharmacological treatment of anxiety disorders (Clum et al. 1993; Cox et al. 1992a,b; Fedoroff and Taylor 2001; Foa 2000; Furukawa et al. 2006; Gould et al. 1997; Mattick et al. 1990; Mitte 2005; van Balkom et al. 1997; Westen and Morrison 2001). The main reasons for these inconsistent results seem to be the inclusion of heterogeneous studies and influences of selection biases (see also Klein 2000). A meta-analysis was performed, which only included studies using a direct comparison of pharmacological, psychological, or combined treatments (Bandelow et al. 2007a). According to this meta-analysis, drug treatment and cognitive behavioural therapy were equally effective, but combined pharmacological and psychological treatment was substantially superior to the monotherapies in panic disorder patients. All in all, there is enough evidence to recommend the combination.

It is believed that gains from CBT are maintained after termination of treatment, while patients on drugs immediately have a relapse of anxiety symptoms after medication is stopped. This would offer CBT considerable advantage over drug treatment. However, an analysis of available follow-up studies comparing the durability of CBT with drug therapy does not clearly show longer "durability" of CBT. In only one of six panic disorder studies, a longer-lasting effect of CBT could be demonstrated (Marks et al. 1993). One study showed superiority of CBT, but the patients in the CBT group were allowed to use benzodiazepines, making the results difficult to interpret (Clark et al. 1994). In one study, drug treatment was superior to CBT at follow-up (Loerch et al. 1999). Three studies did not show a difference between drugs and psychological therapies (Barlow et al. 2000; Cohen et al. 1984; Mavissakalian et al. 1983).

Psychodynamic (psychoanalytic) therapy. Only a few studies have evaluated psychodynamic psychotherapy in panic disorder. In one study, psychodynamic therapy was superior to "applied relaxation", a relaxation technique (Milrod et al. 2007). Some patients received additional SSRI treatment in this trial. Before this treatment modality can be recommended for routine treatment, further studies are needed. As applied relaxation is a therapist-aided relaxation technique, which does not involve systematic therapeutic conversations, psychodynamic therapy should also be compared with a psychological placebo in future studies. As a second step, it should be compared with CBT, as pure psychodynamic therapy was less effective than a combination of psychodynamic therapy and exposure in agoraphobic patients (Hoffart and Martinsen 1990).

Client-centered therapy. Two methodologically problematic studies assessed the efficacy of client-centered therapy. In the first study (Teusch et al. 1997), 40 patients with panic disorder and agoraphobia were assigned to pure client-centered therapy or to additional behavioural exposure treatment. For a short period, the combined treatment was superior in some measures. The second study did not find a difference between the groups (Teusch et al. 2001). As these studies did not involve a control group and did not have enough power to detect treatment differences, their scientific validity is limited.

Eye movement desensitization and reprocessing (EMDR). Eye movement desensitization and reprocessing (EMDR) has been used for panic disorder with disappointing results (Feske and Goldstein 1997; Goldstein et al. 2000).

Exercise. In one study, aerobic exercise (jogging) was more effective than a pill placebo, but less effective than clomipramine (Bandelow et al. 2000). Exercise has been proposed as a remedy for all kinds of psychiatric disorders. However, only a few controlled studies have been performed to assess its usefulness. In the first study examining the role of exercise in an anxiety disorder, patients with panic disorder were randomly assigned to three treatment modalities: running, clomipramine or placebo. Both exercise and clomipramine led to a significant decrease of symptoms in comparison to placebo; however, exercise was still significantly less effective than clomipramine (Bandelow et al. 2000). In a later study, a combination of drug treatment and exercise was investigated. Patients received paroxetine or placebo in a double-blind manner. Additionally, patients in both groups were randomly allocated to exercise or a control group, relaxation training. Whereas paroxetine was superior to placebo, exercise did not differ from the control group, perhaps due to the high effect sizes attained in the latter treatment modality. Taking the results of both studies together, exercise seems to have some effect in panic disorder, however, this effect seems to be less pronounced than the effect of medication (Wedekind et al. submitted).

Table VIII. Summary of Recommendations for the Treatment of Panic Disorder

Recommendation grade	Category of evidence	Treatment
1	A	– SSRIs (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) and the SNRI venlafaxine are the first-line treatment for panic disorder.
2	A	– TCAs (clomipramine, imipramine), are equally effective, but they are less well tolerated than the SSRIs and may be potentially lethal in overdose. – In treatment-resistant cases, benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam) may be used when the patient does not have a history of dependency. Also, they can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants.
3	B	– Due to possible serious side effects and interactions with other drugs and food components, the irreversible MAOI phenelzine should only be prescribed when other first-line drugs have failed or not been tolerated.
4	C1	– For mirtazapine, valproate and inositol, preliminary evidence is available, however, adequate RCTs are lacking
	C1	– According to open studies, ondansetron, bupropion, tiagabine, vigabatrin, milnaciprane, combinations of SSRIs and TCAs, olanzapine monotherapy, augmentation of an SSRI with olanzapine, augmentation of SSRI treatment with pindolol or TCAs, a combination of valproate and clonazepam were effective – In treatment-resistant cases, olanzapine, addition of fluoxetine to a TCA, addition of TCA to fluoxetine, or addition of olanzapine to an SSRI was effective according to open studies
	C2	– In treatment-resistant cases, addition of lithium to clomipramine or a combination of valproate and clonazepam was effective according single case reports
5	D	– Efficacy results with the RIMA moclobemide and the NARI reboxetine were inconsistent
Non-pharmacological treatment		– CBT/exposure therapy for panic disorder/agoraphobia is more effective than a wait list condition and is superior to a psychological/pill placebo in the majority of studies – A combination of CBT and medication is more effective than the monotherapies – There is preliminary evidence for psychoanalytic treatment – There is preliminary evidence for limited usefulness of aerobic exercise

Summary of recommendations for the treatment of panic disorder. The treatment recommendations for panic disorder are summarized in Table VIII.

Generalized anxiety disorder (GAD)

Selective serotonin reuptake inhibitors (SSRIs). Efficacy in double-blind placebo-controlled studies has been demonstrated for some SSRIs.

- *Escitalopram* was superior to placebo (Davidson et al. 2004b; Goodman et al. 2005). In a three-arm study, both escitalopram and paroxetine were superior to placebo (Baldwin et al. 2006). In the above-mentioned comparison with venlafaxine, escitalopram did not separate from placebo on the primary efficacy measure. However, on all secondary analyses escitalopram was superior to placebo (Bose et al. 2007). In a relapse prevention study over 24–76 weeks, escitalopram showed long-term superiority over placebo (Allgulander et al. 2006). Similar results were found in a 24-week relapse prevention study (Montgomery et al. 2005). In a 24-week study, escitalopram and paroxetine were equally effective (Bielski et al. 2005) (A).
- *Paroxetine* was effective in DBPC studies (Pollack et al. 2001; Rickels et al. 2003). Long-term efficacy for paroxetine was established in a 24-week placebo controlled study following an 8-week open treatment with paroxetine (Stocchi et al. 2003) and a 24-week comparison with escitalopram (Bielski et al. 2005)(A).
- *Sertraline* was more effective than placebo (Allgulander et al. 2004a; Brawman-Mintzer et al. 2006). In a comparison of the SSRIs paroxetine and sertraline, both drugs were equally effective and tolerated well (Ball et al. 2005). A small study in children age 5–17 years demonstrated superiority of sertraline over placebo (Rynn et al. 2001) (A).
- In a sample of children and adolescents with mixed anxiety disorders, including GAD, *fluoxetine* was superior to placebo (Birmaher et al. 2003)(B).
- *Fluvoxamine* was effective in a sample of children and adolescents with social phobia, separation anxiety disorder, or generalized anxiety disorder (Ruppasg 2001) (B).

Selective serotonin-norepinephrine reuptake inhibitors (SNRIs). Two SNRIs, venlafaxine and duloxetine, were studied in GAD.

- *Venlafaxine* was superior to placebo (Lenox-Smith and Reynolds 2003; Nimatoudis et al. 2004; Rickels et al. 2000b). In comparator studies, it was more effective than placebo and as effective as pregabalin (Montgomery et al. 2006b) and duloxetine (Hartford et al. 2007; Nicolini et al. 2008). In a further comparator study, it was more effective than buspirone (Davidson et al. 1999); however, scores were only significantly lower for HAM-A psychic anxiety factor, anxious mood, and tension, but not for HAM-A total and CGI for venlafaxine-treated patients than for placebo-treated patients. In a study with diazepam as active control, the benzodiazepine was significantly superior to placebo, but neither dose of venlafaxine-XR was different from placebo on HAM-A total score (Hackett et al. 2003). In a three-arm study, venlafaxine, but not escitalopram, separated from placebo on the primary efficacy measure. However, all secondary analyses suggested that escitalopram and venlafaxine XR are both effective treatments for GAD (Bose et al. 2007). Two studies compared venlafaxine and duloxetine with placebo. Both drugs were superior to placebo and equally effective (see next paragraph). In a study comparing venlafaxine, pregabalin and placebo, only pregabalin, but not venlafaxine was superior to placebo (Andréewitch et al. 2008; Kasper et al. in preparation). The efficacy of venlafaxine was also established in long-term studies over 6 months (Allgulander et al. 2001; Gelenberg et al. 2000; Lenox-Smith and Reynolds 2003). Two DBPC studies were conducted with children and adolescents 6–17 years of age (Rynn et al. 2007b). In one of these studies, venlafaxine was superior to placebo, whereas in the second trial the difference to placebo could not be demonstrated on the primary efficacy measure, but only on some secondary outcome measures (A).
- *Duloxetine* was more effective than placebo in DBPC studies (Koponen et al. 2007; Rynn et al. 2007a, 2008). Also, in three-arm studies, both duloxetine and the comparator venlafaxine were better than placebo (Hartford et al. 2007; Nicolini et al. 2008). Two studies with a placebo and a venlafaxine arm were pooled in order to ensure adequate statistical power for a non-inferiority trial. Duloxetine was found not to be not inferior to venlafaxine (Allgulander et al. 2008). Duloxetine was superior to placebo in a double-blind 26-week extension of open treatment for 26 weeks (Davidson et al. 2007b)(A).

Tricyclic antidepressants (TCAs). *Imipramine* was superior to placebo and as effective as reference drugs (Hoehn-Saric et al. 1988; Rickels et al. 1993)(A).

Benzodiazepines. A number of benzodiazepines have been studied in DSM-defined anxiety disorders.

- *Alprazolam* showed positive results in placebo- and comparator-controlled studies (Elie and Lamontagne 1984; Enkelmann 1991; Hoehn-Saric et al. 1988; Lydiard et al. 1997; Möller et al. 2001)(A).
- *Diazepam* was effective in studies containing a placebo condition (Ansseau et al. 1991; Boyer and Feighner, 1993; Fontaine et al. 1983; Rickels et al. 1993, 1997, 2000a) as well as studies using a comparator with established efficacy (Elie and Lamontagne 1984; Feighner et al. 1982; Jacobson et al. 1985; Rickels et al. 2005; Ross and Matas 1987)(A).
- *Lorazepam* was superior to placebo in the above mentioned comparison with pregabalin (Feltner et al. 2003)(B).
- *Bromazepam* was as effective as hydroxyzine (Llorca et al. 2002)(C1).

Pregabalin. Pregabalin was superior to placebo in a placebo-controlled study (Pohl et al. 2005). In three-arm studies, the drug was compared to placebo and lorazepam (Feltner et al. 2003; Pande et al. 2003), alprazolam (Rickels et al. 2005), and venlafaxine (Montgomery et al. 2006b). On most measures, pregabalin was as effective as the established drugs. Onset of efficacy was faster than with venlafaxine. In another placebo- and venlafaxine-controlled study, only pregabalin, but not venlafaxine, was superior to placebo (Andréewitch et al. 2008). One DBPC trial evaluated pregabalin in elderly GAD patients (aged 65 years and older) and showed that the drug is efficacious and safe in this population (Montgomery et al. 2006a).

In a relapse prevention trial, patients received open-label pregabalin for 8 weeks and were then randomized to pregabalin or placebo for 24 weeks (Feltner et al. 2008). Although the trial had to be terminated prematurely due to safety concerns that later were found to be unwarranted, it was possible to evaluate the study. Patients on pregabalin had significantly lower relapse rates than patients in the placebo group (A).

Quetiapine. The atypical antipsychotic quetiapine is usually prescribed in the treatment of schizophrenia in dosages between 150 and 800 mg/day (Falkai et al. 2005). For the treatment of GAD, lower doses (50–300 mg/day) are adequate. In a placebo-controlled study in patients with GAD, quetiapine was superior to placebo (Khan et al. 2008). Onset of efficacy was already detectible at Week 1.

In a comparator study, quetiapine was superior to placebo and as effective as paroxetine. Onset of action was faster than with paroxetine (Bandelow et al. in preparation). In both studies, quetiapine was effective at 50 and 150 mg/day, which are much lower dosages than those usually given to schizophrenic patients. At present time, the results with quetiapine must be seen as preliminary, as some studies are still ongoing (A).

Buspirone. The 5-HT_{1A}-agonist buspirone is effective in the treatment of generalized anxiety disorder, as could be shown in some controlled studies. Buspirone was superior to placebo in some studies (Davidson et al. 1999; Enkelmann 1991; Pollack et al. 1997) and as effective as benzodiazepines (Feighner et al. 1982; Jacobson et al. 1985; Rickels et al. 1982; Ross and Matas 1987; Strand et al. 1990). However, it was less effective than venlafaxine (Davidson et al. 1999) or hydroxyzine (Lader and Scotto 1998). Experience in long-term treatment was gained in a 24-week comparison of buspirone with abecarnil, a drug that has not been marketed due to its side-effect profile (Pollack et al. 1997)(D).

Antihistamine hydroxyzine. Efficacy of the antihistamine hydroxyzine was established in a DBPC study (Ferreri et al. 1994). In a comparator study, hydroxyzine, but not buspirone, was superior to placebo (Lader and Scotto 1998). In another three-arm study, hydroxyzine was compared to placebo and the benzodiazepine bromazepam (Llorca et al. 2002). The efficacy of hydroxyzine was confirmed, and no differences were found between the two active drugs in terms of efficacy. However, long-term studies are lacking with this drug. Day-time sedation may be a problem (B).

Other Medications

- *Opipramol*, a drug which is similar to tricyclic antidepressants with respect to chemical structure, showed efficacy in a placebo- and comparator-controlled study (Möller et al. 2001). However, this drug is not available in many countries (B).
- *Agomelatine* is an agonist at melatonin receptors and an antagonist at 5-HT_{2C} receptors. The drug has shown efficacy in major depression. In one study in GAD, agomelatine was superior to placebo (Stein et al. 2007a). The most commonly reported side effects are headache, nausea, and diarrhoea, but these adverse events at the same frequency as with placebo. In comparison to other antidepressants, nausea, sexual dysfunctions, weight gain and discontinuation effects were not reported. The evidence for agomelatine must be seen as preliminary, as the drug has not yet been licensed (B).
- *Valproate* was effective in a DBPC study (Aliyev and Aliyev 2008)(B).
- In a small double-blind pilot study, *bupropion* demonstrated comparable anxiolytic efficacy to escitalopram (Bystritsky et al. 2008). However, the power of the study was not sufficient to detect significant differences between the two drugs (C1).
- *Tiagabine*, a selective GABA reuptake inhibitor anticonvulsant, was investigated in DBPC studies, but failed to differentiate from placebo (Pollack et al. 2005, 2008)(E).
- *Propranolol* did not show sufficient evidence in GAD (Meibach et al. 1987)(E).
- *PRX-00023*, a 5-HT_{1A} receptor agonist, failed to show superiority over placebo (Rickels et al. 2008) (E).

Open studies are listed in Table IX.

Table IX. GAD: Open Trials and Case Reports.

Disorder	Drugs	Authors	Efficacy
Generalized anxiety disorder	Paroxetine vs. imipramine vs. chlordemethyl-diazepam	Rocca et al. 1997	all equally effective (C1)
	Selective GABA reuptake inhibitor anticonvulsant tiagabine	Rosenthal 2003	As effective as paroxetine. Not effective in DBPC study (E)
	Azapirone buspirone	Feighner 1987	yes (1 year). Inconsistent results in RCTs (D)

Homeopathic formulations and herbal preparations

- A *Ginkgo biloba* extract was superior to placebo; however, the sample did not consist of pure GAD patients, but was a mixed sample of patients with generalized anxiety disorder and adjustment disorder with anxious mood (Woelk et al. 2007).
- In the only DBPC study of a *homeopathic formulation* in GAD, no difference to placebo was found (Bonne et al. 2003)(E).
- *Kava kava* extracts were not effective in GAD (Connor and Davidson 2002; Connor et al. 2006b) and have been taken from the market due to hepatotoxicity, which was perhaps due to failure in the production of the plant extracts (E).

Long-term treatment. GAD is generally a chronic disorder and requires long-term treatment. In many patients, GAD has a waxing and waning course. After remission, treatment should continue for at least several months in order to prevent relapse. Expert consensus conferences generally recommend a duration of pharmacotherapy of at least 12 months (Allgulander et al. 2003). In recent years, a number of controlled maintenance studies with a duration of 6–12 months also suggest treatment to be continued for this period, as significantly more relapses occurred in the patients treated with placebo. Treatment with escitalopram, paroxetine, venlafaxine, duloxetine, and pregabalin was more effective in preventing relapses than placebo (see above for references).

Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed. Such failure should be clearly documented in the notes.

Treatment of GAD in children and adolescents. In above-mentioned studies, sertraline was effective in children adolescents, whereas the results with venlafaxine were inconsistent.

Treatment-resistant GAD. A few studies investigated the addition of atypical antipsychotics in patients remaining symptomatic despite initial anxiolytic treatment.

- In a placebo-controlled trial with treatment-refractory GAD patients, adjunctive *risperidone* was associated with significant improvement (Brawman-Mintzer et al. 2005) (B).
- In patients who remained symptomatic remaining symptomatic on fluoxetine, augmentation with *olanzapine* was superior to adjunctive placebo (Pollack et al. 2006) (B).
- One preliminary study with a small sample size did not support the addition of *quetiapine* to continued paroxetine CR for individuals with GAD who remain symptomatic after 10 weeks of prospective antidepressant pharmacotherapy (Simon et al. 2008b)(E).

Non-pharmacological treatment. As a psychological treatment strategy, *cognitive behaviour therapy* (CBT) and associated techniques have been used in generalized anxiety disorder. Cognitive behavioural therapy is based on cognitive models stressing the role of worrying, meta-cognitions, and avoidance behaviour.

A number of studies showed superiority of CBT to a waiting list group (Barlow et al. 1992; Butler et al. 1991; Dugas et al. 2003; Ladouceur et al. 2000; Lindsay et al. 1987; Mohlman et al. 2003). Moreover, comparisons with a "psychological placebo", a pill placebo or comparable control group conditions showed that CBT has not only unspecific psychotherapy effects, but also specific ingredients (Borkovec et al. 1987; Borkovec and Costello 1993; Linden et al. 2005; Power et al. 1990; Stanley et al. 2003). In one study, CBT for GAD was superior to a wait list, but was not more effective than a psychological placebo (Wetherell et al. 2003).

Standard CBT was shown to be as effective as other behavioural treatment modalities, such as "Applied Relaxation" (Arntz 2003; Öst and Breitholtz 2000) or "Anxiety Management" (Durham et al. 1994; Lindsay et al. 1987). Cognitive therapy was superior to "pure" behaviour therapy (Butler et al. 1991). In a comparison with *psychoanalytic treatment*, CBT was more effective (Durham et al. 1994). Also, stability of treatment effects with CBT could be shown at 12-month follow-up (Borkovec and Costello 1993).

Comparisons of psychological and pharmacological therapies and their combination. Data on the advantages of combining drugs and psychological therapy are almost completely lacking. In particular, comparisons between standard drugs for GAD and psychotherapy are lacking. One study found no gains in combining buspirone and CBT (Lader and Scotto 1998); however, the statistical power of this study may have been too low. In another study, the combination of CBT and diazepam was more effective than diazepam alone (Power et al. 1990).

When GAD is comorbid with depression, which is more the rule than the exception, pharmacotherapy with antidepressants is more strongly indicated (Ballenger et al. 2001).

Summary of recommendations for the treatment of GAD. A summary of recommendations for the treatment of GAD is given in Table X.

Social phobia (social anxiety disorder, SAD)

Selective serotonin reuptake inhibitors (SSRIs). SSRIs were effective in a number of trials in SAD.

- *Escitalopram* was effective in a DBPC study in social anxiety disorder (Kasper et al. 2005). A long-term study over 24 weeks showed equal efficacy of escitalopram and paroxetine and superiority to placebo (Lader et al. 2004). In a relapse prevention study, responders of 12 weeks open treatment were randomized to treatment with escitalopram or placebo for 24 weeks. Escitalopram was more effective in preventing relapses (Montgomery et al. 2005)(A).
- *Fluvoxamine* and fluvoxamine CR (controlled release) were effective in DBPC studies (Asakura et al. 2007; Davidson et al. 2004a; Stein et al. 1999; van Vliet et al. 1994; Westenberg et al. 2004). In a long-term study patients were again randomized to fluvoxamine CR or placebo for a 12-week extension. The primary efficacy measure did not reach statistical significance, while fluvoxamine differed from placebo on secondary measures (Stein et al. 2003b)(A).
- *Paroxetine* was effective in a number of DBPC studies (Allgulander 1999; Baldwin et al. 1999; Lepola et al. 2004; Liebowitz et al. 2002a; Pollack et al. 2001; Stein et al. 1998). Also, in two placebo-controlled comparator studies, paroxetine was as effective as venlafaxine (Allgulander et al. 2004b; Liebowitz et al. 2005a). In a social phobia study with children and adolescents 12–17 years of age, paroxetine was superior to placebo (Wagner et al. 2004). In small DBPC studies in patients with a double diagnosis of SAD and alcohol use, paroxetine showed an effect on social anxiety and on alcohol use (Book et al. 2008; Randall et al. 2001). In a relapse prevention study, responders were randomized to a further 24 weeks of paroxetine or placebo in the extension of a 12-week single-blind treatment with paroxetine. Relapse rates were significantly lower in the paroxetine group (Stein et al. 2002b)(A).
- *Sertraline* has been shown to be effective in DBPC studies: (Blomhoff et al. 2001; Katzelnick et al. 1995; van Ameringen et al. 2001). The efficacy has also been shown in the long term. In one 24-week DBPC study (Blomhoff et al. 2001) and a 24-week relapse prevention study (Walker et al. 2000) following a 20-week DBPC study (van Ameringen et al. 2001), the efficacy of sertraline could be demonstrated (A).
- *Citalopram* was effective in one DBPC study (Furmark et al. 2005)(B).
- Two DBPC studies with *fluoxetine* did not show superiority over placebo (Clark et al. 2003; Kobak et al. 2002). However, in another study, fluoxetine was more effective than placebo (Davidson et al. 2004c). In a sample of children and adolescents with mixed anxiety disorders,

Table X. Summary of Recommendations for the Treatment of GAD.

Recommendation grade	Category of evidence	Treatment
1	A	– The drugs recommended as the first-line treatment for GAD are the SSRIs (escitalopram, paroxetine, and sertraline), the SNRIs (venlafaxine and duloxetine), and the calcium channel modulator pregabalin – Results with the atypical antipsychotic quetiapine were positive; however, the results are preliminary
2	A	– The TCA imipramine is effective in GAD, but its potential lethality in case of overdose, as well as the lower tolerability, puts it as a second-line option. – In treatment-resistant cases, benzodiazepines (alprazolam, diazepam) may be used when the patient does not have a history of dependency. Also, they can be combined with antidepressants in the first couple of weeks of treatment before the onset of efficacy of the antidepressants – The antihistamine hydroxyzine was effective in placebo- and comparator-controlled studies; however, the drug has sedating properties
3	B	– For opipramol and valproate, limited positive evidence is available – In treatment-refractory GAD patients, augmentation of SSRI treatment with atypical antipsychotics (risperidone or olanzapine) may be used
4	D	– Efficacy results with buspirone were inconsistent
Non-Pharmacological Treatment		– CBT is more effective than a wait list control and a "psychological placebo"

including social phobia, fluoxetine was superior to placebo (Birmaher et al. 2003)(D).

Selective serotonin-norepinephrine reuptake inhibitors (SNRIs). In a small DBPC study, the efficacy of the immediate-release (IR) formulation of *venlafaxine* was shown (Katzelnick et al. 1995). Also, the efficacy of the extended release (XR) formulation was shown in DBPC trials in adults (Liebowitz et al. 2005b; Rickels et al. 2004) and children and adolescents (March et al. 2007). In a comparison with paroxetine, venlafaxine XR was as effective as paroxetine, while both active drugs were better than placebo (Allgulander et al. 2004b; Liebowitz et al. 2005a). In a 6-month relapse-prevention study venlafaxine was superior to placebo (Stein et al. 2005) (A).

Irreversible monoamine oxidase inhibitors (MAOIs). The irreversible MAOI *phenelzine* was superior to placebo, atenolol and moclobemide (Heimberg et al. 1998; Liebowitz et al. 1988; Versiani et al. 1992). Long-term efficacy was shown in a comparison of phenelzine and moclobemide; however, phenelzine was less well tolerated than moclobemide (Versiani et al. 1992). All in all, MAOIs present a viable option in non-responsive SAD (A).

Reversible inhibitor of monoamine oxidase A (RIMA) moclobemide. Results with *moclobemide* are inconsistent. The compound was superior to placebo in two studies (IMCTGMSP 1997; Stein et al. 2002a) and also more effective than placebo and as effective as phenelzine on most measures in a third (Versiani et al. 1992). In a fourth study, the size of its clinical effect was small (Schneier et al. 1998), and in fifth study (Noyes et al. 1997), no superiority against placebo could be demonstrated. Two long-term studies have been conducted with moclobemide. In a 24-week study, both phenelzine and moclobemide were superior to placebo (Versiani et al. 1992). In an extension of a 12-week double-blind study, patients could continue treatment for an additional 6 months. Both in the acute and the long-term treatment phase, moclobemide was superior to placebo (Stein et al. 2002a).

In a meta-analysis, response rates and effects sizes for RIMAs were smaller than those seen for SSRIs (van der Linden et al. 2000)(D).

Benzodiazepines. The benzodiazepine *clonazepam* was superior to placebo or a waiting list condition in two studies (Davidson et al. 1993b; Munjack et al. 1990)(B).A combination of paroxetine and clonazepam in SAD did not show a faster response in comparison with paroxetine (and placebo), while in the same time, this combination showed a trend better outcome than paroxetine plus placebo (Seedat and Stein 2004). The power of the study was perhaps insufficient to detect a significant difference.

Beta-blockers. Despite their wide-spread use in social anxiety, the only extant studies do not show superiority of the beta-blocker *atenolol* over placebo (Liebowitz et al. 1988; Turner et al. 1994). Findings with the treatment of performance anxiety in musicians (James and Savage 1984; James et al. 1983) should not be generalized to social anxiety disorder (E).

Other medications.

– The NaSSA (noradrenergic and specific serotonergic antidepressant) *mirtazapine* was effec-

Table XI. Social Anxiety Disorder (SAD): Open Trials and Case Reports.

Disorder	Drugs	Authors	Efficacy
Social phobia			
	SSRI citalopram	Bouwer and Stein 1998	Yes. Effective in DBPC study (B)
	SSRI fluvoxamine	DeVane et al. 1999	Yes. Effective in DBPC studies (A)
	SSRI fluoxetine	Gorman et al. 1987; van Ameringen et al. 1993	Yes. Inconsistent results in DBPC studies (D)
	TCA imipramine	Simpson et al. 1998	No (E)
	MAOI tranylcypromine	Versiani et al. 1988	Yes. Effective in DBPC studies (A)
	Anticonvulsant tiagabine	Dunlop et al. 2007	Yes (C1)
	Anticonvulsant topiramate	Van Ameringen et al. 2004	Yes (C1)
	Anticonvulsant levetiracetam	Simon et al. 2004	Yes (C1)
Social phobia, treatment-resistant			
	SNRI venlafaxine	Altamura et al. 1999	Yes (C1)
	Addition of buspirone to an SSRI	van Ameringen et al. 1996	Yes (C1)
	SSRI escitalopram	Pallanti and Quercioli 2006	Yes (C1)
Social phobia in children and adolescents			
	SSRI escitalopram	Isolan et al. 2007	Yes. Effective in DBPC studies (A)

tive in female patients with SAD in a DBPC study (Muehlbacher et al. 2005)(C1).
- Both *gabapentin* (B) and *pregabalin* (D) were shown to be effective in SAD in DBPC studies (Pande et al. 1999, 2004). In an unpublished study, pregabalin was not effective in SAD.
- The atypical antipsychotic *olanzapine* was superior to placebo in a small pilot study with seven evaluable patients (Barnett et al. 2002) (C1).
- The neurokinin-1 antagonist *GR205171* was effective in a DBPC study (Furmark et al. 2005) (C1).
- In an underpowered study with 15 patients, *quetiapine* did not separate from placebo (Vaishnavi et al. 2007)(E).
- The results of a DBPC study did not support the efficacy of the azapirone anxiolytic *buspirone* in social anxiety disorder (van Vliet et al. 1997) (E).

For open trials with other compounds, see Table XI.

Long-term treatment. SAD is generally a chronic disorder and requires long-term treatment.Expert consensus conferences generally recommend a duration of pharmacotherapy of at least 12 months. In recent years, a number of controlled maintenance studies with a duration of 6–12 months also suggest treatment to be continued for this period, as significantly more relapses occurred in the patients treated with placebo. Escitalopram, paroxetine, sertraline, venlafaxine, phenelzine and moclobemide were more effective than placebo in preventing relapses (see above for references).

Treatment of children and adolescents. Efficacy of SSRIs *fluoxetine* and *paroxetine* and the SNRI *venlafaxine* could be shown for in the above-mentioned studies. The results with *CBT* were mixed (see below).

Treatment-resistant social phobia. Pindolol augmentation of paroxetine was not successful in a DBPC study with SAD patients non-responsive to standard treatment (Stein et al. 2001)(E).

Open studies with treatment-resistant patients are listed in Table XI.

Non-pharmacological treatment. Among psychological therapies, exposure therapy and cognitive therapy have been shown to be effective. Some studies found variations of CBT techniques to be more effective than a wait list condition: CBT and exposure plus applied relaxation (Clark et al. 2006), self-exposure with or without cognitive therapy (Salaberria and Echeburua 1998), group CBT (Mortberg et al. 2006), group CBT and exposure (Hofmann 2004), internet-based cognitive-behavioural therapy (Carlbring et al. 2006).

Only few studies found superiority of CBT for social phobia to a "psychological placebo" (Cottraux et al. 2000; Heimberg et al. 1990) or a pill placebo (Davidson et al. 2004c). Two studies did not find a difference between active treatment and placebo control (Smits et al. 2006; Turner et al. 1994). One study did not find superiority of exposure to "general medical care" (Blomhoff et al. 2001); however, in this study exposure was not performed by professional psychotherapists.

In children and adolescents with SAD, CBT was more effective than a wait-list control condition in two studies (Baer and Garland 2005; Spence et al. 2000), while another study did not find lasting effects (Hayward et al. 2000).

Comparisons of psychological and pharmacological therapies and their combination. In one study comparing the efficacy of phenelzine and CBT, phenelzine was superior to CBT in the acute and maintenance treatment phase, but phenelzine patients showed a trend toward greater relapse during treatment-free follow-up (Heimberg et al. 1998; Liebowitz et al. 1999). In a second study of the same work group, which has not yet been published, phenelzine, CBT, and a combination of both were compared. A preliminary evaluation showed moderate advantages for the combination (Zaider and Heimberg 2004).

In another placebo-controlled study, sertraline, exposure therapy, and their combination were compared. Sertraline-treated patients improved significantly more than non-sertraline-treated patients. No significant difference was observed between exposure- and non-exposure-treated patients. Although the combination showed higher effect sizes than both treatment modalities alone, the difference was not statistically significant (Blomhoff et al. 2001).

In a follow-up of this study, patients were re-examined after a treatment-free period of 28 weeks. Exposure patients only reached the degree of improvement that the sertraline patients already had during the acute study. Improvement was also shown in the placebo group, so that the effects were probably due to spontaneous remission (Bandelow 2004; Bandelow and Haug 2004; Haug et al. 2003).

In one study, patients received CBT, fluoxetine plus self-exposure, or placebo plus self-exposure. CBT was superior to the two other conditions, while fluoxetine showed no effect (Clark et al. 2003). One study compared fluoxetine, cognitive

behavioural group therapy, placebo, and the combinations of CBT plus fluoxetine and CBT plus placebo. All treatments were superior to placebo, but did not differ among themselves (Davidson et al. 2004c).

A comparison of moclobemide, CBT plus pill placebo and the combination moclobemide and CBT had mixed results with some advantages for moclobemide in the first 3 months, but no advantage of the combination after 6 months (Prasko et al. 2006a). There was no control condition for CBT. The combination of CBT and pharmacotherapy yielded the most rapid effect.

In an open study, individual CBT was superior to group CBT and "treatment as usual" with SSRIs (Mortberg et al. 2007).

According to a meta-analysis of studies with both a psychological and a drug treatment arm, there is only preliminary support for combined treatment for social anxiety disorder (Bandelow et al. 2007a).

In a meta-analysis on treatments of children with SAD, symptoms of social anxiety and impairment were reduced by both CBT and SSRI treatment, with higher effect sizes for SSRIs (Segool and Carlson 2007).

Altogether, due to methodological limitations of comparison studies, the question still remains open whether CBT/exposure and medications have synergistic effects.

A number of studies suggests that d-cycloserine, a partial *N*-methyl-d-aspartate (NMDA) receptor agonist, might facilitate fear extinction and exposure therapy by either enhancing NMDA receptor function during extinction or by reducing NMDA receptor function during fear memory consolidation, according to a meta-analysis (Norberg et al. 2008). In social anxiety disorder, augmentation of exposure therapy with d-cycloserine was successful according to two studies (Guastella et al. 2008; Hofmann et al. 2006).

Summary of recommendations for social anxiety disorder. Recommendations for the treatment of SAD are summarized in Table XII.

Specific phobia

Usually, patients with specific phobia do not consult psychiatrists or other medical professionals, especially if they can cope with their phobia by avoiding the specific feared situations or objects. Only when there are significant restrictions in the quality of life, they will seek professional advice. Exposure therapy is effective to treat specific phobia (Marks 1987). Psychopharmacological drugs are not recognized as a standard treatment in simple cases of specific phobia. However, when specific phobia leads to substantial restrictions in quality of life, drug treatment should be tried.

- In a small preliminary study, *paroxetine* was superior to placebo (Benjamin et al. 2000)(B).
- In a very small study with only 12 evaluable patients, *escitalopram* showed numerical superiority to placebo, which did not reach statistical significance, probably due to lack of test power (Alamy et al. 2008) (F).

Summary of recommendations for specific phobia. Recommendations for the treatment of SAD are summarized in Table XIII.

Table XII. Summary of Recommendations for the Treatment of SAD.

Recommendation grade	Category of evidence	Treatment
1	A	– The drugs recommended as the first-line treatment for SAD are the SSRIs (escitalopram, fluvoxamine, paroxetine and sertraline) and the SNRI venlafaxine
2	A	– The MAOI phenelzine is effective in SAD, but is less well tolerated than other antidepressants
3	B	– In treatment-resistant cases, benzodiazepines (clonazepam) may be used when the patient does not have a history of dependency. Also, they can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants. – For citalopram and gabapentin, preliminary positive evidence is available
4	C1	– For olanzapine, tranylcypromine, tiagabine, topiramate and levetiracetam, preliminary evidence is available, but adequate RCTs are lacking In treatment-resistant cases, addition of buspirone to an SSRI was effective according to an open study
5	D	– Efficacy results with moclobemide were inconsistent
Non-pharmacological treatment		– CBT/exposure is more effective than a wait list control condition, and more effective than a psychological/pill placebo in some, but not all studies – The efficacy of exposure therapy for social anxiety disorder could be enhanced by augmentation with d-cycloserine

Table XIII. Summary of Recommendations for the Treatment of Specific Phobia.

Recommendation grade	Category of evidence	Treatment
1	B	– The SSRI paroxetine was effective in treating specific phobia
Non-pharmacological treatment		– Exposure therapy is effective

Obsessive compulsive disorder (OCD)

This overview is mainly focused on the treatment of "pure" OCD and does not cover OCD-spectrum disorders such as tic disorders, Gilles-de-la-Tourette syndrome, trichotillomania, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and others.

The treatment of obsessive compulsive disorder is usually associated with lower response rates than the treatment of anxiety disorders. Sometimes only partial remission is achieved.

Selective serotonin reuptake inhibitors (SSRIs). A number of studies have been performed to assess the efficacy of SSRIs in the treatment of OCD.

- In a three-arm study, *escitalopram* was superior to placebo, as was the reference drug paroxetine (Stein et al. 2007b). In a relapse prevention study, patients with OCD were treated with open label escitalopram for 16 weeks, after which the responders were randomized to placebo or escitalopram. The proportion of patients that relapsed was statistically significantly higher in the placebo group (Fineberg et al. 2007) (A).
- *Fluvoxamine* was and found to be superior to placebo in DBPC studies (Goodman et al. 1989b, 1996; Hohagen et al. 1998; Nakatani et al. 2005) and in clomipramine-controlled trials (Milanfranchi et al. 1997; Mundo et al. 2000). The slow-release form was also superior to placebo (Hollander et al. 2003c). In a small study, which was probably underpowered, fluvoxamine was significantly better than placebo on only two of three measures of improvement in obsessive-compulsive symptoms (Jenike et al. 1990). In the treatment of children and adolescents, the efficacy of fluvoxamine could also be shown in DBPC studies (Riddle et al. 1996, 2001) (A).
- *Fluoxetine* was superior to placebo in double-blind studies (Montgomery et al. 1993; Tollefson et al. 1994; Zitterl et al. 1999). In a comparison with clomipramine, efficacy for both drugs was comparable, with a minor advantage for clomipramine (Lopez-Ibor et al. 1996). In a one-year DBPC study, only patients on the highest dose of fluoxetine (60 mg) showed significantly lower relapse rates; however, the study was underpowered (Romano et al. 2001). In a comparison of fluoxetine and phenelzine with placebo, efficacy was shown for fluoxetine but not the MAOI (Jenike et al. 1997). Efficacy of fluoxetine could also be shown for the treatment of OCD in children and adolescents in DBPC studies (Geller et al. 2001; Liebowitz et al. 2002b; Riddle et al. 1992) (A).
- *Paroxetine* was significantly more effective than placebo and of comparable efficacy to clomipramine (Zohar and Judge 1996). Paroxetine was also found to be effective in the DBPC comparison with escitalopram (Stein et al. 2007b). Efficacy of paroxetine was also shown in a relapse prevention study. Patients who had received open-label paroxetine for 6 months following a 12-week DBPC study were then randomized to paroxetine or placebo. Under paroxetine treatment, relapses were significantly less frequent (Hollander et al. 2003a). A small DBPC study by (Kamijima et al. 2004) suggests paroxetine is also effective across different cultural settings. Efficacy of paroxetine in OCD could also be shown in a DBPC study in children and adolescents (Geller et al. 2004). In a relapse prevention study, children and adolescents with OCD were treated openly for 16 weeks and then randomized to either paroxetine or placebo for 16 weeks. The study failed to differentiate between placebo and paroxetine on relapse measures, possibly because the duration of follow-up was too short (Geller et al. 2003) (A).
- *Sertraline* was effective in DBPC (Chouinard et al. 1990; Greist et al. 1995a; Kronig et al. 1999) and clomipramine-controlled (Bisserbe et al. 1997) studies. Long-term studies showed efficacy over 1 year in a DBPC study (Greist et al. 1995b) and a 1-year open-label extension (Rasmussen et al. 1997). In a relapse prevention trial, patients who met criteria for response after 16 and 52 weeks of a single-blind trial of sertraline were randomly assigned to a 28-week double-blind trial of sertraline and placebo. Sertraline had significantly greater efficacy than placebo on two of three primary outcomes (Koran et al. 2002). The efficacy of sertraline

could be demonstrated in studies with children and adolescents suffering from OCD (March et al. 1998; Pediatric OCD Treatment Study Group 2004) (A).
– *Citalopram* was effective in a DBPC study (Montgomery et al. 2001) (B).

Dosage recommendations are overviewed in Table VI. As a rule, higher doses of the antidepressants are used in OCD, as compared with other anxiety disorders or major depression. Fixed-dose comparator studies provide inconsistent evidence for a dose–response relationship with SSRIs, higher doses being associated with greater efficacy in most (Hollander et al. 2003a; Montgomery et al. 1993; Romano et al. 2001; Stein et al. 2007b) but not all evaluations (Greist et al. 1995b; Tollefson et al. 1994). In the study by Montgomery et al. higher doses of citalopram were more efficacious on secondary but not primary efficacy measures (Montgomery et al. 2001). However, in these clinical studies, only doses within the normal range were used. In non-responders, greater symptom improvement was seen with higher doses (see below).

Tricyclic antidepressants (TCAs). Efficacy has been shown for the TCA *clomipramine* in DBPC studies (Clomipramine Collaborative Study Group 1991; DeVeaugh Geiss et al. 1989; Thoren et al. 1980) as well as in comparator trials (Milanfranchi et al. 1997) (see (Piccinelli et al. 1995) for a review). In a 1-year DBPC study, clomipramine demonstrated the same efficacy as in short-term trials (Katz et al. 1990). Clomipramine efficacy could also be demonstrated in DBPC studies in children and adolescents with OCD (DeVeaugh-Geiss et al. 1992; Flament et al. 1985)(A).

The available evidence based on eight head-to-head comparisons suggests that there are no differences in efficacy between clomipramine and SSRIs (Zohar and Kindler 1992), and contradicts other (not head-to-head) studies which propose that clomipramine has greater anti-obsessional efficacy than do the SSRIs (Abramowitz 1997; Bisserbe et al. 1997; Greist et al. 1995c; Piccinelli et al. 1995; Pigott and Seay 1999; Todorov et al. 2000). Some direct comparisons suggest that SSRIs are better tolerated than clomipramine while having the same efficacy (Bisserbe et al. 1997; Milanfranchi et al. 1997; Mundo et al. 2000; Zohar and Judge 1996; Zohar 2008).

The 5-HT reuptake profile seems to be a crucial for efficacy in OCD, as TCAs with predominant 5-HT reuptake inhibition, such as clomipramine, are more effective than desipramine, a drug blocking predominantly norepinephrine reuptake (Zohar and Insel 1987).

Other medications.

– The MAOI *phenelzine* was as effective as clomipramine in one small study (Vallejo et al. 1992), but less effective than fluoxetine and no better than placebo in another (Jenike et al. 1997)(D).
– *Mirtazapine* was superior to placebo in double-blind discontinuation period after an open trial (Koran et al. 2005b)(B). Adding mirtazapine to citalopram did not result in increased efficacy when compared to addition of placebo, but was associated with a faster onset of efficacy, according to a single-blind study (Pallanti et al. 2004).
– In a DBPC study, *venlafaxine* was not effective; however, the sample size, the dose and the study duration were insufficient in this trial (Yaryura-Tobias and Neziroglu 1996). While more patients improved with venlafaxine than with placebo, a substantial number of patients on active drug even showed a worsening of symptoms. In a non-placebo double-blind cross-over study, venlafaxine was as effective as paroxetine (Denys et al. 2003)(D).
– The second messenger precursor *inositol* was superior to placebo in a cross-over trial with 13 patients, but these results have to be regarded as preliminary due to the low sample size in the study (Fux et al. 1996). In a DBPC cross-over study with only 10 patients, no significant difference was found between the two treatment phases (Fux et al. 1999)(D).
– A DBPC study failed to support the efficacy of *St John's wort* in OCD (Kobak et al. 2005) (E).

Serotonin reuptake inhibition seems to be a necessary condition for a drug to be effective in OCD. In direct comparisons, compounds with predominant norepinephrine reuptake inhibition, such as desipramine (Hoehn-Saric et al. 2000; Leonard et al. 1989) or nortriptyline (Thoren et al. 1980) were less effective than drugs with a serotonin reuptake component.

Long-term treatment. OCD requires long-term treatment. In long-term and relapse prevention studies, escitalopram, fluoxetine, paroxetine, sertraline and clomipramine were superior to placebo (see above for references).

Within the limits of the acute treatment phase, response to treatment with SSRIs is characteristi-

Table XIV. Obsessive Compulsive Disorder (OCD): Open Trials and Case Reports

Disorder	Drugs	Authors	Efficacy
OCD			
	Citalopram	Koponen et al. 1997; Thomsen 1997	Yes. Effective in DBPC study (B)
	SSRI escitalopram	Galvao-de Almeida et al. 2007	Yes. Effective in DBPC studies (A)
	SNRI venlafaxine, SSRI fluoxetine	Kocabasoglu et al. 2004	Venlafaxine =fluoxetine
	SNRI venlafaxine, TCA clomipramine	Albert et al. 2002	Lower response rate with venlafaxine than with clomipramine. Incosisten results in DBPC studies (D)
	Addition of gabapentin to an SSRI	Onder et al. 2008	No (E)
	Aripiprazole	Connor et al. 2005	Yes (C1)
	Hallucinogen psilocybin	Moreno et al. 2006	Yes (C1)
	Nicotine chewing gum	Lundberg et al. 2004	Yes (C1)
	Naloxone infusion	Keuler et al. 1996	No (E)
	Cyproterone acetate	Casas et al. 1986	Yes (C1)
	rTMS	Greenberg et al. 1997; Mantovani et al. 2006	Yes/partially (C1)
OCD in children			
	Citalopram	Thomsen 1997; Mukaddes et al. 2003	Yes. Effective in DBPC study (B)
	Paroxetine	Rosenberg et al. 1999	Yes. Effective in DBPC studies (A)
	Sertraline	Wagner et al. 2003	Yes. Effective in DBPC studies (A)
	Glutamate antagonist riluzole	Grant et al. 2007	Yes (C1)
OCD, treatment-resistant			
	SSRI citalopram	Marazziti et al. 2001	Yes (C1)
	Glutamate antagonist riluzole	Coric et al. 2005	Yes (C1)
	NMDA receptor antagonist memantine	Pasquini and Biondi, 2006; Poyurovsky et al. 2005	Yes (C2)
	Gonadotropin-releasing hormone analogue triptorelin	Eriksson 2007	Yes (C1)
	Naltrexone	Gade et al. submitted	Yes (C2)
	SSRI citalopram+NARI reboxetine	Fontenelle et al. 2005	Yes (C2)
	Addition of clomipramine to an SSRI	Pallanti et al. 1999	Yes (C1)
	Addition of an SSRI to clomipramine	Ravizza et al. 1996	Yes (C1)
	Adding lithium to clomipramine*	Rasmussen 1984	Yes (C1)
	Addition of buspirone to an* SSRI	Jenike et al. 1991b; Markovitz et al. 1990	Yes (C1)
	Addition of topiramate to an SSRI	Hollander and Dell'Osso, 2006; Van Ameringen et al. 2006	Yes (C1)
	Addition of *N*-acetylcysteine to an SSRI	Lafleur et al. 2006	Yes (C2)
	Addition of atypical antipsychotics – aripiprazole, – olanzapine, – perospirone, – quetiapine, or – risperidone, to an SSRI or clomipramine	Agid and Lerer 1999; Atmaca et al. 2002; Bogan et al. 2005; Bogetto et al. 2000; da Rocha and Correa 2007; Dell'Osso et al. 2006; Francobandiera, 2001; Friedman et al. 2007b; Kawahara et al. 2000; Koran et al. 2000; Marazziti and Pallanti 1999; Marazziti et al. 2005; Mohr et al. 2002; Otsuka et al. 2007; Pfanner et al. 2000; Ravizza et al. 1996; Saxena et al. 1996; Stein et al. 1997; Storch et al. 2008; Weiss et al. 1999; Yoshimura et al. 2006	Yes (C1)

Table XIV (*Continued*)

Disorder	Drugs	Authors	Efficacy
	Addition of l-tryptophan to clomipramine or to SSRI + pindolol	Blier and Bergeron 1996; Rasmussen 1984	Yes (C1)
	Addition of inositol to an SSRI	Seedat and Stein 1999	No (E)
	Electroconvulsive therapy	Gruber 1971; Husain et al. 1993; Khanna et al. 1988; Maletzky et al. 1994; Mellman and Gorman 1984	Yes (C1)
OCD in children, treatment-resistant			
	Adding clonazepam or risperidone to an SSRI	Leonard et al. 1994	Yes (C2)
	Adding risperidone to an SSRI	Fitzgerald et al. 1999	Yes (C2)

cally partial. Between 30 and 60% cases in acute phase DBPC studies reached a clinically relevant level of improvement. However, according to a DBPC study, responder rates increased to 70% by 24 weeks (Stein et al. 2007b). During the open-label phase of a DBPC relapse prevention trial, 78% cases achieved clinical response status by the 16 week endpoint (Fineberg et al. 2007). Gains may even accrue for at least 2 years (Rasmussen et al. 1997).

In a 7-year follow-up of a study after treatment with CBT in combination with either fluvoxamine or placebo in a randomized design, 29 of 30 patients still needed additional psychotherapy and/or medication. This might indicate that OCD patients usually require ongoing treatment to maintain their improvements over long periods (Rufer et al. 2005).

Taken together, these results suggest that OCD requires long-term treatment at an effective dose-level and that continuation of SSRI protects patients against relapse. The possibility that some patients may retain response at a lower dose or following drug-discontinuation must be weighed against the possibility that reinstatement of treatment after relapse may be associated with a poorer response.

Treatment of OCD in children and adolescents. Similar to the treatment of adults, the efficacy of the SSRIs fluvoxamine, fluoxetine, paroxetine, and sertraline and the TCA clomipramine could be confirmed in studies with children and adolescents suffering from OCD (see above). Regarding doses of the SSRIs, it has been suggested that maintenance treatment should be on a medium to high dose (Romano et al. 2001).

Augmentation strategies have been tried in treatment-resistant cases (Table XIV).

Non-pharmacological treatment of OCD in children is based on psychosocial interventions such as family education and cognitive-behavioural therapy. Behavioural treatment strategies involving exposure and relapse prevention are considered most effective (Rapoport and Inoff-Germain 2000).

In a comparison of CBT alone, sertraline alone, combined CBT and sertraline, or pill placebo, all active groups were superior to placebo. Combined treatment also proved superior to CBT alone and to sertraline alone, which did not differ from each other (Pediatric OCD Treatment Study Group 2004).

Treatment-resistant obsessive-compulsive disorder. About 40% OCD patients treated with SSRIs fail to fully respond to treatment and continue to exhibit significant symptoms.

Two studies used doses higher than the normal range in non-responders. In a double-blind study comparing sertraline 200 mg/day with higher doses

(250–400 mg/day), greater symptom improvement was seen in the high-dose group (Ninan et al. 2006). In an open-label study, patients who did not respond to escitalopram 20 mg/day showed improvement after a dosage increase (maximum 50 mg/day) (Rabinowitz et al. 2008).

Many alternative treatments, some of which have been experimental, have been tried in these sometimes desperate cases.

- In double-blind studies, *intravenous clomipramine* was more effective than oral clomipramine (Fallon et al. 1998; Koran et al. 1997)(B).
- Augmentation of antidepressant treatment may be tried for patients with a partial response or intolerance to higher doses of antidepressant. Many studies have assessed the effectiveness of antipsychotic augmentation in SSRI-refractory OCD. In a DBPC study, adding *haloperidol* to an SSRI (McDougle et al. 1994) appeared to provide an improved response particularly in patients with comorbid chronic tic disorders (B). In DBPC studies, the combination of the atypical antipsychotics *quetiapine, olanzapine and risperidone* with an SSRI was more effective than SSRI monotherapy (Bystritsky et al. 2004; Denys et al. 2004a; Erzegovesi et al. 2005; Hollander et al. 2003b; McDougle et al. 2000; Shapira et al. 2004)(B). In a small study, adding quetiapine to an SSRI was more effective than adding placebo, however, the difference did not reach statistical significance (Fineberg et al. 2005). One study failed to show benefits of quetiapine augmentation (Carey et al. 2005)(E). In a double-blind cross-over study, both haloperidol and risperidone were as effective when added to an SSRI (Li et al. 2005). A comparison of risperidone and olanzapine augmentation to an SSRI revealed no difference between the two drugs (Maina et al. 2008). Altogether, meta-analyses demonstrated positive effects of antipsychotic augmentation (Bloch et al. 2006; Fineberg et al. 2006; Skapinakis et al. 2007). The subgroup of OCD patients with comorbid tics had a particularly beneficial response to this intervention. Other patients that had benefit from the combination were those with poor insight (Hollander et al. 2003b) and co-occurring schizotypal personality disorder (Bogetto et al. 2000; McDougle et al. 1990). There is also evidence suggesting OCD patients should be treated with at least 3 months of maximal-tolerated therapy of an SSRI before initiating antipsychotic augmentation owing to the high rate of treatment response to continued SSRI monotherapy. However, only one-third of treatment-refractory OCD patients showed a meaningful treatment response to antipsychotic augmentation. In summary, there was sufficient evidence demonstrating the efficacy of haloperidol and risperidone; however, evidence regarding the efficacy of quetiapine and olanzapine is inconclusive, according to a review (Bloch et al. 2006). Notably, there have been several case reports on OCD symptoms in schizophrenic patients induced by antipsychotics (Zohar et al. 2006).
- A DBPC study did not demonstrate any additional effect for *buspirone* augmentation to clomipramine (Pigott et al. 1992)(E).
- The addition of *pindolol* to paroxetine treatment was successful in a DBPC study (Dannon et al. 2000)(B), but the addition of pindolol to fluvoxamine had no effect (Mundo et al. 1998)(E).
- In a small double-blind cross-over study ($n = 28$), patients who were resistant to clomipramine treatment improved with the benzodiazepine *clonazepam* (Hewlett et al. 1992)(C1). Addition of clonazepam to sertraline was not effective in a DBPC study (Crockett et al. 2004)(E).
- A double-blind cross-over study compared *morphine*, *lorazepam*, and placebo in treatment-refractory patients with OCD. Only one patient on morphine showed sufficient response (Koran et al. 2005a)(C2).
- In a small DBPC cross-over study with 10 treatment-refractory patients, the opioid antagonist *naltrexone* did not improve OCD symptoms, but even led to and exacerbation of anxiety and depression (Amiaz et al. 2008)(E).
- In a DBPC study, a statistically significant reduction in symptoms was noted after *lithium* augmentation of ongoing fluvoxamine treatment, although most patients did not have a clinically meaningful response, according to the authors (McDougle et al. 1991)(E).

A number of other augmentation strategies were studied in open-label trials. These are summarized in Table XIV.

There are only few "switching" studies, i.e. studies that investigate the switch from one drug to another. In one double-blind study, the switch from venlafaxine to paroxetine and *vice versa* was investigated in non-responders. Overall, 42% of the patients showed improvement after the switch; 56% of the venlafaxine-nonresponders improved with paroxetine. Conversely, only 19% of the paroxetine-non-

responders showed benefits from the switch (Denys et al. 2004b). In a case series, switching from an SSRI to the SNRI duloxetine was successful in a number of treatment-resistant patients (Dell'osso et al. 2008).

Non-pharmacological treatment. Cognitive behaviour therapy (CBT)/exposure and response prevention (ERP). Cognitive behaviour therapy (CBT) and exposure and response prevention (ERP) have been investigated in clinical studies in patients with OCD.

Two studies showed the superiority of CBT to a wait list condition (Cordioli et al. 2003; Freeston et al. 1997). Also, in children and adolescents, ERP was superior to a wait list (Bolton and Perrin 2008). Controlled studies comparing CBT or ERP with "psychological placebo" control conditions seem to be rare. In one study, clinician-guided behaviour therapy was compared to behaviour therapy via internet telephone and relaxation as control group. Clinician-guided therapy was more effective than internet therapy, and both CBT treatments were more effective than relaxation (Greist et al. 2002). In another study, ERP was superior to "anxiety management" as a control group, but only 18 patients were included in the study (Lindsay et al. 1997). In one study, ERP was superior to a pill placebo (Foa et al. 2005).

Mostly, elements of cognitive therapy and ERP are combined in clinical settings. Some studies evaluated whether these techniques differ in efficacy. CBT was superior to ERP in one study (van Oppen et al. 1995), whereas CBT and ERP were found to be equal in other studies (McLean et al. 2001; Vogel and Gotestam 2004; Whittal et al. 2005).

A significant proportion of OCD patients refuse treatment or terminate treatment programs early, because they fear high levels of revulsion or anxiety or even "magical" consequences when not performing rituals. Moreover, even among those who do complete treatment, a substantial proportion of people do not respond. CBT treatment requires a triad of a specialist in the treatment of OCD, a strong motivation and compliance of the patient and a substantial time investment.

Comparisons of psychological and pharmacological therapies and their combination. The results of studies comparing drugs (clomipramine or SSRIs) with CBT or ERP are not easy to interpret.

One study with a complicated cross-over design that involved clomipramine, placebo, exposure in vivo and relaxation, both clomipramine and exposure had positive effects on different symptoms of OCD (Marks et al. 1980). In another complex study involving self-exposure, clomipramine, and therapist-aided exposure, self-exposure was the most potent; clomipramine played a limited adjuvant role, and therapist-aided exposure a marginal one (Marks et al. 1988). A comparison of fluvoxamine with antiexposure, fluvoxamine with exposure, or placebo with exposure was difficult to interpret. Both fluvoxamine and exposure improved different symptoms of OCD and showed some transient synergistic effects (Cottraux et al. 1990; Cottraux et al. 1993). A combination of an SSRI, fluvoxamine, with CBT was associated with a higher response rate than CBT alone (Hohagen et al. 1998). In a cross-over comparison of cognitive therapy, exposure, fluvoxamine plus cognitive therapy, fluvoxamine plus exposure, and a waiting list control condition, all four treatment packages were equally effective (van Balkom et al. 1998). However, the sample sizes may have been too small to detect differences. Moreover, the combination groups received only 10 therapy sessions that started after 8 weeks of fluvoxamine treatment, whereas the groups receiving exposure or CT alone received 16 therapy sessions. In a double-blind trial comparing exposure and ritual prevention, clomipramine, their combination (exposure and ritual prevention plus clomipramine), and pill placebo, the effect of exposure and ritual prevention did not differ from that of exposure and ritual prevention plus clomipramine, and both were superior to clomipramine only (Foa et al. 2005). However, there was no control condition for exposure, this limiting the validity of the findings. One study compared CBT $\pm$ pill placebo, autogenic training (a psychological placebo for OCD) $\pm$ fluvoxamine and autogenic training $\pm$ pill placebo. Patients in the CBT group had the highest improvement scores, followed by fluvoxamine, which was still significantly superior to placebo (Nakatani et al. 2005).

In a follow-up study, cognitive therapy (CT) alone, exposure in vivo with response prevention (ERP) alone, and CBT (either CT or ERP) in combination with fluvoxamine were compared. After 5 years, 54% of the participants no longer met criteria for OCD. Long-term outcome did not differ between the three treatment groups. Compared with patients receiving CT alone, significantly more patients receiving CBT with fluvoxamine used antidepressants 5 years later (van Oppen et al. 2005).

In a comparison of CBT and sertraline, CBT was more effective (Sousa et al. 2006). However, the dosage of sertraline in this study did not exceed 100 mg/day and there was no control for time spent with the CBT therapist. Two small studies compared CBT, CBT plus medication, medication alone and placebo. In the first protocol, 21 patients were

randomly allocated to either fluvoxamine or placebo condition for a 5-month period. Both groups subsequently received CBT for a further 5 months. In the second protocol, 22 patients received CBT; one group was already stabilized on an antidepressant of choice, the second group was drug-naive. All active treatments showed clinical improvement. There was no difference in treatment response to CBT regardless of whether participants had previously received medication or placebo. CBT had a more specific anti-obsessional effect than medication but CBT plus medication showed greatest overall clinical improvement (O'Connor et al. 2006). In a study comparing the addition of CBT to drug treatment with drug treatment alone, greater effects were seen in the combination group. However, there was no control condition for CBT (Tenneij et al. 2005). Drug non-responders showed improvement with CBT in an uncontrolled study (Tolin et al. 2004).

In a naturalistic 6–43 months follow-up of patients receiving fluvoxamine or clomipramine, CBT/ERP, or ERP with concurrent SSRI medication, no differences in OCD symptom severity were found among the three treatment groups (Hembree et al. 2003). A follow-up 12 weeks after treatment discontinuation showed lower relapse rates in responders to exposure alone or exposure plus clomipramine than in responders to clomipramine alone (Simpson et al. 2004).

Studies comparing drugs and CBT in children and adolescents are described in the section ("OCD in children and adolescents").

d-Cycloserine, a glutamatergic partial *N*-methyl-d-aspartate (NMDA) agonist, can facilitate extinction learning related to cued fear in animals and humans. It was hypothesized that d-cycloserine could enhance the effects of CBT. However, the results of DBPC studies in OCD were disappointing (Kushner et al. 2007; Storch et al. 2007; Wilhelm et al. 2008)(E).

In summary, the results of studies comparing drugs (clomipramine or SSRIs) with CBT or ERP are inconclusive. The emerging impression is that there is no clear advantage for either strategy, and although the usefulness of a combination of both modalities was not clearly supported or rejected. The usefulness of a combination of both modalities was not clearly supported or rejected, the clinical utility of exposure in any anxiety disorder and also in OCD seems undeniable. An individual patient with poor response should receive a trial with both modalities. With greater severity of OCD, it may be advisable to add medications (Cottraux et al. 2005).

Electroconvulsive therapy (ECT). Clinical consensus is that there is a very limited role for ECT in the treatment of OCD, and that it is limited to symptomatic treatment of OCD comorbidities, namely depression, catatonia, etc., and might be helpful for these symptoms rather than to the core OCD pathology. Electroconvulsive therapy has been tried in a number of studies in patients with OCD (Table XIV). These uncontrolled studies showed response at least in some of the patients.

Repetitive transcranial magnetic stimulation (rTMS). In double-blind studies with sham rTMS as control, rTMS over the left dorsolateral prefrontal cortex was ineffective (Prasko et al. 2006b; Sachdev et al. 2007). Also, right prefrontal rTMS failed to produce significant improvement of OCD and was not significantly different from sham treatment. The use of a relatively nonfocal, teardrop-shaped coil limits the interpretation of the results (Alonso et al. 2001). In one study, compulsive urges, but not obsessions, decreased significantly, and positive mood increased moderately with right lateral prefrontal rTMS, but not after left rTMS or occipital rTMS (Greenberg et al. 1997).

Neurosurgery. In severe OCD cases, where all other available therapeutic approaches have been tried without success, neurosurgery may be a treatment option. Only unblinded studies are available that showed improvements after

- *bilateral anterior capsulotomy* (Lippitz et al. 1999; López Ibor and López-Ibor Aliño 1975; Mindus et al. 1990, 1999; Oliver et al. 2003; Rück, 2006; Skoog and Skoog 1999),
- *cingulotomy* (Baer et al. 1995; Dougherty et al. 2002; Jenike et al. 1991a; Kim et al. 2003; Richter et al. 2004),
- *limbic leucotomy* (Cumming et al. 1995; Hay et al. 1993; Montoya et al. 2002; Sachdev and Hay 1995),
- *subcaudate tractotomy* (Hodgkiss et al. 1995; Woerdeman et al. 2006) or
- *thalamotomy/pallidotomy* (Jeanmonod et al. 2003).

Side effects may vary according to the surgical technique. For some patients these may be particularly serious (including headache, weight-gain/loss, nausea/vomiting, urinary disturbances, insomnia, apathy, hypomania, transitory hallucinations, epileptic seizure, progressive behaviour disorder, reduced intellectual, emotional, memory and cognitive functions, and death by suicide). In a follow-up of five patients after neurosurgery, all patients failed to

maintain initial improvements after surgery and relapsed. In addition, they became depressed with suicidal ideation or attempt (Yaryura-Tobias et al. 2000). In a long-term follow-up of 25 consecutive OCD capsulotomies, only two patients achieved remission, while severe side effects were observed in a substantial number of patients (Rück 2006). According to these studies, the risk–benefit ratio of capsulotomy for OCD is not acceptable.

The advent of gamma knife radiosurgery (anterior capsulotomy) for OCD has permitted the design of blinded, controlled studies. Preliminary results were promising (Lopes et al. 2008).

The availability of reversible and adjustable DBS may lead to a decrease in the use of ablative neurosurgical procedures. However, neurosurgery procedures still may represent a potentially efficacious alternative for a few carefully selected patients with very severe and refractory OCD.

Deep brain stimulation (DBS). Deep brain stimulation is a promising new technology that has been tried in neurology, usually on much older patients. Its utility in OCD is still to be evaluated. DBS is non-ablative neurosurgery, and as such still involves a brain operation.

In a case series, DBS in both anterior limbs of the internal capsules was successful (Anderson and Ahmed 2003; Gabriels et al. 2003; Nuttin et al. 1999; Nuttin et al. 2003). Deep brain stimulation (DBS) of the anterior limb of the internal capsule was still effective after three years, according to an open study (Greenberg et al. 2006). DBS of the ventral caudate nucleus was effective in the treatment of a patient with obsessive-compulsive disorder and major depression (Aouizerate et al. 2004). In treatment-refractory patients with OCD, dramatic improvement was seen in one patient out of four (Abelson et al. 2005). When using the right nucleus accumbens as a target for DBS, improvements were seen in OCD (Sturm et al. 2003).

Summary of recommendations for the treatment of OCD. The treatment recommendations for OCD are summarized in Table XV.

Post-traumatic stress disorder (PTSD)

Selective serotonin reuptake inhibitors (SSRIs). SSRIs have been regarded as first-line drugs in PTSD. Efficacy has been shown in DBPC studies for the following SSRIs:

- *Fluoxetine* was effective in DBPC studies (Connor et al. 1999; Martenyi et al. 2002b; Meltzer-Brody et al. 2000; van der Kolk et al. 1994, 2007). One study failed to differentiate between fluoxetine and placebo (Martenyi et al. 2007). In another placebo-controlled study with only 12 patients, no effect of fluoxetine could be shown, but the study did not have enough power to be conclusive (Hertzberg et al. 2000). In a relapse prevention study, patients who responded to 12 weeks of acute treatment with fluoxetine were re-randomized and continued in a 24-week phase with fluoxetine or placebo (Martenyi et al. 2002a). In a relapse-prevention study, subjects received open-label treatment for 6 months followed by double-blind randomized treatment with fluoxetine or placebo for 6 months: fluoxetine was superior to placebo (Davidson et al. 2005). Fluoxetine was also superior to placebo in a 24-week relapse-prevention trial after a 12-week acute study (Martenyi and Soldatenkova 2006)(A).
- *Paroxetine* was effective in DBPC studies (Marshall et al. 2001; Tucker et al. 2001)(A).
- *Sertraline* was effective in a number of DBPC studies (Brady et al. 2000; Davidson et al. 2001b; Stein et al. 2006; Zohar et al. 2002). One trial did not find a difference between sertraline and placebo (Friedman et al. 2007a). In one placebo-controlled study, sertraline was not effective, in contrast to venlafaxine (Davidson et al. 2006b). A comparison of sertraline and nefazodone, a drug that has been withdrawn from the market in many countries, did not reveal differences among both drugs (McRae et al. 2004). In a relapse-prevention study, patients who had responded to 24 weeks of open-label treatment with *sertraline* were randomized to either sertraline or placebo for an additional 28 weeks. Relapse rates were significantly lower in the sertraline group (Davidson et al. 2001a). In an open-label study, patients who had completed 12-week DBPC studies of sertraline versus placebo received sertraline for an additional 24 weeks. Responders to the DBPC study sustained their initial response, and patients who failed in the initial study could become responders (Londborg et al. 2001)(A).
- The SSRI *fluvoxamine* was as effective as *reboxetine*, a norepinephrine reuptake inhibitor (Spivak et al. 2006)(C1).

For open-label studies, see Table XVI.

Selective serotonin norepinephrine reuptake inhibitors (SNRI). In the above-mentioned placebo-controlled study in patients with PTSD, *venlafaxine* was more effective than placebo, in contrast to sertraline

Table XV. Summary of Recommendations for the Treatment of OCD

Recommendation grade	Category of evidence	Treatment
1	A	– SSRIs (escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) are the first-line treatment for OCD.
2	A	– The TCA clomipramine is equally effective, but is less well tolerated than the SSRIs
3	B	– Citalopram and mirtazapine were effective in a DBPC studies – In treatment-resistant cases, intravenous clomipramine was more effective than oral clomipramine, and the combination of the antipsychotics haloperidol, quetiapine, olanzapine and risperidone with an SSRI was more effective than SSRI monotherapy
4	C1	– According to open studies, the following treatments were effective: aripiprazole and some experimental treatments such as cyproterone acetate, the hallucinogen psilocybin, and nicotine chewing gum – In treatment resistant cases, the following medications were successful: the glutamate antagonist riluzole, the NMDA receptor antagonist memantine, and the gonadotropin-releasing hormone analogue triptorelin, SSRI citalopram+NARI reboxetine, addition of clomipramine to an SSRI or vice versa, adding lithium to clomipramine, addition of buspirone to an SSRI, addition of topiramate to an SSRI, and addition of l-tryptophan to clomipramine or to SSRI+pindolol
5	D	– Efficacy results with the MAOI phenelzine, the SNRI venlafaxine, and the second messenger precursor inositol were inconsistent
Non-pharmacological treatment		– CBT/ERP is more effective than a wait list condition and superior to a psychological/pill placebo – The usefulness of a combination of CBT/ERP and medications was not clearly supported or rejected. – Electroconvulsive therapy may be effective in some patients, but should be restricted to carefully selected treatment-refractory sufferers from OCD. It may be helpful in treating some relevant symptoms in specific patients, i.e. incapacitating depression, catatonia, etc. – Results with repetitive transcranial magnetic stimulation (rTMS) were mostly negative – Neurosurgery and deep brain stimulation (DBS) were only tried in uncontrolled studies in a few patients. The results were mixed. However, these procedures may represent a potentially effective alternative for a few carefully selected patients with very severe OCD. Some authors find that the risk-benefit-ratio of neurosurgery for OCD is not acceptable.

(Davidson et al. 2006b). In a long-term study over 24 weeks, venlafaxine was more effective in the treatment of PTSD than placebo (Davidson et al. 2006a)(A).*Tricyclic antidepressants (TCAs)*. A number of studies investigated efficacy of TCAs in PTSD.

- Double-blind studies found *amitriptyline* to be superior to placebo (Davidson et al. 1990, 1993a)(B).
- In a comparison with phenelzine, *imipramine* was superior to placebo. It was as effective as phenelzine on the CGI, but less effective on one scale (Kosten et al. 1991). Another small study showed equal efficacy for *phenelzine* and *imipramine* (Frank et al. 1988)(B).
- In a small cross-over study, response to the tricyclic *desipramine* was only with respect to depression, but not for anxiety and PTSD symptoms (Reist et al. 1989)(E).

In comparison to the SSRIs, TCAs are associated with a higher incidence of side effects, risk of overdose, and poor compliance rates.

Benzodiazepines. In the only placebo-controlled trial of benzodiazepines in PTSD, improvement in anxiety symptoms was significantly greater with *alprazolam* than with placebo but modest in extent. Symptoms specific to PTSD were not significantly altered. However, the sample size of this study (10 patients, cross-over) was too small to draw definite conclusions (Braun et al. 1990)(F).

Monoamine oxidase inhibitors (MAOI). *Phenelzine* has been studied and shown to be effective in the above-mentioned comparisons with imipramine (Frank et al. 1988; Kosten et al. 1991). It was shown to be effective with a rather significant effect size. One study that failed to show a difference between phenelzine and placebo was underpowered, and the treatment duration (4 weeks) was probably too short (Shestatzky et al. 1988)(D).

Other medications.

- In a small DBPC study, the antidepressant *mirtazapine* was effective (Davidson et al. 2003)(B).
- The atypical antipsychotic *risperidone* was effective in DBPC studies (Monnelly et al. 2003; Padala et al. 2006)(B). One DBPC study showed a modest effect on psychotic symptoms in PTSD for adjunctive risperidone (Hamner et al. 2003b).
- The anticonvulsant and mood stabilizer *lamotrigine* has been studied in a small study and showed a higher response rate in comparison to placebo (Hertzberg et al. 1999)(B).
- The α_1-antagonist *prazosin* was effective in a small DBPC study with 10 patients (Raskind et al. 2003)(C1).
- *Bupropion* was not different from placebo (Becker et al. 2007) (E).
- The anticonvulsant *valproate* was not effective in a DBPC study (Davis et al. 2008a) (E).
- The selective GABA reuptake inhibitor anticonvulsant *tiagabine* did not seem to have an effect (Connor et al. 2006a; Davidson et al. 2007a) (E).
- Assuming hyperactivity of the norepinephrine system in patients with PTSD, the α_2-adrenergic agonist *guanfacine* was tested in PTSD, but the results were negative (Davis et al. 2008b; Neylan et al. 2006) (E).

For open trials, see Table XVI.

Long-term treatment. PTSD is often a chronic disorder and needs long-term treatment for at least 12–24 months. Long-term efficacy was proven for SSRIs fluoxetine and sertraline and the SNRI venlafaxine (see above for references).

Treatment-resistant post-traumatic stress disorder. In a DBPC study, adjunctive *olanzapine* was effective in SSRI-resistant patients with PTSD (Stein MB et al. 2002) (B). According to a DBPC study, addition of *risperidone* to ongoing treatments for PTSD was successful as well (Monnelly et al. 2003) (B). However, in another DBPC study, the augmentation of sertraline therapy with *risperidone* did not show additional benefits on the primary, but did on some secondary measures (Rothbaum et al. 2008)(E).

For open studies, see Table XVI.

Secondary prevention of PTSD. Not all persons subject to severe traumatic events develop PTSD. The percentage of affected persons varies between 15 and 50%, depending on the kind of trauma. Prophylactic treatments have been suggested for preventing the emergence of post-traumatic symptoms in people subject to major trauma.

- Acute intravenous administration of hydrocortisone was superior to placebo in preventing emergence of post-traumatic symptoms, both in intensive care patients with septic shock and in patients undergoing cardiac surgery (Schelling et al. 2001, 2004)(B).

Table XVI. Post-Traumatic Stress Disorder (PTSD): Open Trials and Case Reports.

Disorder	Drugs	Authors	Efficacy
PTSD			
	SSRI citalopram	Seedat et al. 2000; Seedat et al. 2001	Yes (C1)
	SSRI escitalopram	Robert et al. 2006	Yes (C1)
	SSRI fluvoxamine	Davidson et al. 1998; Escalona et al. 2002; Marmar et al. 1996; Neylan et al. 2001	Yes. Effective in DBPC study (C1)
	SSRI paroxetine	Marshall et al. 1998	Yes. Effective in DBPC studies (A)
	TCA desipramine	Reist et al. 1989	No (E)
	Moclobemide	Neal et al. 1997	Yes (C1)
	Trazodone	Warner et al. 2001	Effect on nightmares; no report on overall symptomatology
	Quetiapine	Hamner et al. 2003a	Yes (C1)
	Olanzapine	Petty et al. 2001	Yes (C1)
	Anticonvulsant phenytoin	Bremner et al. 2004	Yes (C1)
	Anticonvulsant carbamazepine	Lipper et al. 1986	Moderate (C1)
	Anticonvulsant gabapentin	Hamner et al. 2001	Yes (C1)
	Anticonvulsant lamotrigine	Berlant and van Kammen 2002	Yes. Effective in DBPC study (B)
	Anticonvulsant topiramate	Berlant and van Kammen 2002; Berlant 2001	Yes (C1)
	Anticonvulsant valproate	Fesler 1991	Moderate. Not effective in DBPC study (E)
	NMDA receptor antagonist memantine	Battista et al. 2007	Yes (C1)
	Fluoxetine, moclobemide, or tianeptine	Onder et al. 2006	Yes, all equal (C1)
	Fluoxetine vs. amitriptyline	Cavaljuga et al. 2003	Response 70% with amitriptyline, 60% with fluoxetine (C1)
	Propranolol and hypnotics	Pastrana Jiménez et al. 2007	Yes
	Addition of triiodothyronine (T3) to an SSRI	Agid et al. 2001	Yes (C2)
	Addition of quetiapine to venlafaxine	Sattar et al. 2002	Yes (C2)
	Imipramine+clonidine	Kinzie and Leung 1989	Yes (C1)
	Addition of gabapentin to an SSRI	Malek-Ahmadi 2003	Yes (C2)
	Addition of levetiracetam to antidepressant therapy	Kinrys et al. 2006	Yes (C1)
	Non-benzodiazepine zolpidem	Dieperink and Drogemuller 1999	Effect on insomnia
PTSD, treatment-resistant	SNRI venlafaxine	Hamner and Frueh 1998	Yes, but inconsistent results in DBPC studies (D)
	α_1-Antagonist prazosin	Peskind et al. 2003; Raskind et al. 2000; Raskind et al. 2002; Taylor and Raskind 2002	Only effective in nightmares (C1)
Prevention of PTSD	Beta-blocker propranolol	Taylor and Cahill 2002; Vaiva et al. 2003	Yes. Not effective in DBPC study (E)
Prevention of PTSD in children	Beta-blocker propranolol	Famularo et al. 1988	Partly. Not effective in DBPC study (E)

- Acute administration of propranolol was superior to placebo in reducing subsequent post-traumatic symptoms and physiological hyperactivity to reminders of trauma, but not the emergence of PTSD (Pitman et al. 2002)(E).
- In a small study comparing propranolol, pregabalin and placebo, neither study drug showed a significant benefit over placebo on depressive or posttraumatic stress symptoms (Stein MB et al. 2007) (E).
- Early administration of benzodiazepines after trauma did not prevent the emergence of post-traumatic symptoms and actually might even be associated with a less favorable outcome (Gelpin et al. 1996; Mellman et al. 2002)(E).

Non-pharmacological treatment. Cognitive behavioural therapy. Cognitive behaviour therapy (CBT) was superior to a wait list control (Blanchard et al. 2003; Cloitre et al. 2002; Foa et al. 1991, 1999;

Keane et al. 1989; Resick et al. 2002; Taylor et al. 2003). Superiority to a psychological placebo was found in a number of studies (Blanchard et al. 2003; Bryant et al. 2003; Echeburua et al. 1997; Marks et al. 1998; Power et al. 2002). In some studies CBT was superior to a wait list control, but not more effective than a psychological placebo (Foa et al. 1991; McDonagh et al. 2005; Neuner et al. 2004).

Regarding the special technique of behavioural therapy, there have been some conflicting research findings, as confrontation with trauma-related stimuli may also have negative effects. Exposure therapy showed positive results in some, but a deterioration in some other studies (Shalev et al. 1996).

In order to prevent the development of PTSD, "debriefing", a therapeutic conversation with an individual who has just experienced a traumatic event, was attempted. However, several studies showed a *worsening* in the debriefing groups when compared to a control group (Bisson et al. 1997; Deahl et al. 2000; Hobbs et al. 1996; Mayou et al. 2000), while two studies did not show a difference (Conlon et al. 1999; Rose et al. 1999). Also, a meta-analysis of debriefing showed that it does not improve natural recovery from trauma-related disorders (van Emmerik et al. 2002). Thus, a single-session debriefing is no longer considered a treatment of choice, nor a harmless intervention.

Eye movement desensitization and reprocessing therapy (EMDR). In an EMDR session, the client is instructed to focus on an image of a traumatic memory. Then the therapist moves his fingers to the end of the patient's field of vision, while the patients moves her/his eyes following the therapist's fingers. Some therapists use sounds, tapping, or tactile stimulations.

EMDR was superior to a wait list condition (Jensen 1994; Lee et al. 2002; Rothbaum 1997; Vaughan et al. 1994), to a psychological placebo (Carlson et al. 1998; Marcus et al. 1997; Power et al. 2002; Scheck et al. 1998; Taylor et al. 2003) or a pill placebo (van der Kolk et al. 2007).

In two comparisons of CBT/exposure and EMDR, the latter was less effective (Devilly and Spence 1999; Taylor et al. 2003). In another comparison with exposure, both treatments were equal, but the study was underpowered (Ironson et al. 2002).

Argument has revolved around whether the eye movements or other distraction elements in the EMDR protocol are a necessary condition or may be superfluous in terms of the contribution to treatment outcome. The effectiveness of EMDR was thoroughly reviewed by the UK National Institute for Clinical Excellence (NICE 2005) and can be summarized as follows: The effectiveness of *EMDR* was generally supported by the meta-analysis, but the evidence base was not as strong as that for trauma-focused CBT, both in terms of the number of RCTs available and the certainty with which clinical benefit was established. The EMDR treatments showed clinically important benefits on clinician-rated PTSD symptom criteria compared with waiting lists. There was only limited evidence for its effectiveness in self-report measures of PTSD symptoms and PTSD diagnosis, for clinically important effects on anxiety and depression, and for superiority to supportive/non-directive therapy.

Repetitive transcranial magnetic stimulation (rTMS). Repetitive transcranial magnetic stimulation was effective in one controlled study (Cohen et al. 2004).

Comparisons of psychological and pharmacological therapies and their combination. There have been very few direct comparisons of the efficacy of psychological and pharmacological treatments, in either acute or long-term treatment. A small unblinded 12-week comparison of paroxetine and CBT suggested that CBT may have certain advantages in reducing post-traumatic and depressive symptoms (Frommberger 2004). In a study investigating the effects of paroxetine augmentation in non-responders to exposure therapy, no additional benefits were found for paroxetine in comparison to placebo. However, the sample size of 23 patients may have been too small to detect differences in treatment-resistant patients (Simon et al. 2008a). In some patients, addition of exposure therapy to sertraline led to further reductions in PTSD severity in an open study (Rothbaum et al. 2006).

In a comparison of EMDR, fluoxetine, and pill placebo, EMDR showed the best results, followed by fluoxetine (van der Kolk et al. 2007).

Summary of recommendations for the treatment of post-traumatic stress disorder. The treatment recommendations for PTSD are summarized in Table XVII.

Treatment under special conditions

Pregnancy

The risks of drug treatment during pregnancy must be weighed against the risk of withholding treatment for an anxiety disorder, OCD or PTSD.

According to the majority of studies, the use of SSRIs and TCAs in pregnancy imposes no increased risk for malformations (Altshuler et al. 2001; Alwan et al. 2007; Austin and Mitchell 1998; Emslie and Judge 2000; Ericson et al. 1999; Hogberg and Wang

Table XVII. Summary of Recommendations for the Treatment of PTSD

Recommendation grade	Category of evidence	Treatment
1	A	– SSRIs (fluoxetine, paroxetine, sertraline) and the SNRI venlafaxine are the first-line treatments for PTSD
3	B	– Amitriptyline, imipramine, mirtazapine, risperidone, and lamotrigine were effective in DBPC trials. Prazosin may reduce nightmares
		– In treatment-resistant cases, adjunctive olanzapine or risperidone were successful
		– Acute intravenous administration of hydrocortisone was superior to placebo in preventing emergence of post-traumatic symptoms in intensive care patients
4	C1	– According to open studies, the following treatments were effective: citalopram, escitalopram, fluvoxamine, moclobemide, tianeptine, quetiapine, olanzapine, phenytoin, carbamazepine, gabapentin, lamotrigine, topiramate, memantine, addition of triiodothyronine (T3) to an SSRI, and imipramine+clonidine
		– In treatment-resistant cases, venlafaxine and prazosin were successful
	C2	– In single cases, addition of quetiapine to venlafaxine ort addition of gabapentin to an SSRI were effective
5	D	– Efficacy results with the MAOI phenelzine were inconsistent
Non-pharmacological treatment		– CBT was superior to wait list control conditions and to a psychological placebo; however, a few studies did not show differences to placebo conditions
		– Exposure therapy showed positive results in some, but a deterioration in some other studies
		– The usefulness of a combination of both modalities cannot be clearly supported or rejected due to lack of data.
		– "Debriefing" is contraindicated
		– There is only limited evidence showing that the effects of EMDR are superior to attention effects
		– rTMS was effective in one controlled study

2005; Kallen and Otterblad Olausson 2007; Koren et al. 2005; Lattimore et al. 2005; Malm et al. 2005; Misri et al. 2000a; Misri et al. 2000b; Nordeng and Spigset 2005; Ramos et al. 2008), although some reports have raised concerns about fetal cardiac effects, newborn persistent pulmonary hypertension, respiratory distress and other effects (ACOG 2006; Oberlander et al. 2008). However, it is recommended to avoid paroxetine use among pregnant women or women planning to become pregnant, if possible (ACOG 2006).

Preschool age children exposed to fluoxetine *in utero* did not show significant neurobehavioural changes (Goldstein and Sundell 1999). The findings of a prospective controlled study suggest that long-term prenatal exposure to tricyclic antidepressants or fluoxetine does not adversely affect cognition, language development or temperament (Nulman et al. 2002).

The anticonvulsants valproate and carbamazepine, but not lamotrigine, were associated with an increased rate of congenital anomalies, as well as neonatal problems (Austin and Mitchell, 1998).

An association between the use of benzodiazepines and congenital malformations has been reported (Laegreid et al. 1990). However, there has been no consistent proof that benzodiazepines may be hazardous. The available literature suggests that it is safe to take diazepam or chlordiazepoxide during pregnancy. It has been suggested that it would be prudent to avoid alprazolam during pregnancy (Iqbal et al. 2002). To avoid the potential risk of congenital defects, physicians should use those benzodiazepines that have long safety records.

Breast feeding

SSRIs and TCAs are excreted into breast milk, and low concentrations have been found in infants' serum (Misri et al. 2000b; Simpson and Noble 2000; Spigset and Hägg 1998). A systematic review indicates that plasma levels of the SSRIs paroxetine and sertraline and the TCA nortriptyline in breast-fed infants levels are usually undetectable, whereas citalopram and fluoxetine produce infant plasma levels that are above 10% of the maternal plasma level in 22 and 17% of infants, respectively (Weissman et al. 2004). In mothers receiving TCAs (with the exception of doxepine), it seems unwarranted to recommend that breast feeding should be discontinued. Fluoxetine was associated with behaviour changes in two breast-fed infants (Spigset and Hägg 1998). Treatment with other SSRIs (citalopram, fluvoxamine, paroxetine or sertraline) seems to be compatible with breast feeding, although this view

Table XVIII. Efficacy of Medications in Children and Adolescents with Anxiety Disorders and OCD in RCTs. Categories of Evidence: See Table II.

Drug	GAD	SAD	Separation anxiety disorder	Overanxious disorder	Avoidant disorder	OCD
Fluvoxamine	(RUPPASG 2001) (B)	RUPPASG 2001 (B)	RUPPASG 2001 (B)			Riddle et al. 1996; Riddle et al. 2001 (A)
Fluoxetine	Birmaher et al. 2003 (B)	Birmaher et al. 2003 (B)	Birmaher et al. 2003 (B)			Geller et al. 2001; Liebowitz et al. 2002b; Riddle et al. 1992 (A)
Paroxetine		Wagner et al. 2004 (B)				Geller et al. 2003; Geller et al. 2004 (D)
Sertraline	Rynn et al. 2001					March et al. 1998; Pediatric OCD Treatment Study Group 2004(A)
Venlafaxine	Rynn et al. 2007b (D)					
Clomipramine						DeVeaugh-Geiss et al. 1992; Flament et al. 1985(A)
Alprazolam				Simeon et al. 1992 (E)	Simeon et al. 1992 (E)	

should be considered as preliminary due to the lack of data (Spigset and Hägg 1998).

Regarding anxiolytic benzodiazepines, adverse drug reactions in newborn infants have been described during maternal treatment with diazepam. During maternal treatment with all benzodiazepines, infants should be observed for signs of sedation, lethargy, poor suckling, and weight loss, and if high doses have to be used and long-term administration is required, breast feeding should probably be discontinued (Iqbal et al. 2002; Spigset and Hägg 1998).

Treating children and adolescents

Regarding the pharmacological treatment of anxiety disorders and OCD, experience in children and adolescents suggests that SSRIs should be the first-line treatment in children and adolescents. In Table XVIII, the studies on drug treatment of children and adolescents are summarized. A meta-analysis of treatments for anxiety disorders in children revealed that the SSRIs were superior to placebo, whereas TCAs and benzodiazepines were not (Dieleman and Ferdinand 2008).

It should be mentioned that the use of SSRIs in children and adolescents has been debated recently, and there have been warnings against their use due to concerns about increased risk of suicidal ideation and behaviour (Hetrick et al. 2007; Scahill et al. 2005). In 2003, the FDA issued a public health warning stating that preliminary evidence showed SSRIs and related antidepressants might be associated with excess reports of suicidality. Later, the FDA tempered the warning with a statement that both untreated depression and treatments for depression lead to suicidality. Some analyses found that SSRIs exhibit efficacy for treatment of depression in children and adolescents (Sharp and Hellings 2006) and found no significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon et al. 2006). However, the FDA warning may have been associated with reduced antidepressant prescriptions and increased suicide rates in children and adolescents (Gibbons et al. 2007). Concerns regarding major depression may not apply to the treatment of children and adolescents with anxiety disorders, OCD and PTSD, as they were not studied. Also, the risk of self-harm is less and the therapeutic benefits greater. Nevertheless, careful monitoring is advisable, due to possible diagnostic uncertainty and the presence of co-morbid depression. Some clinicians also think that it may be preferable to reserve pharmacological treatments for patients who do

not respond to evidence-based psychological approaches.

Treatment of the elderly

Factors that should be regarded in the treatment of the elderly include an increased sensitivity for anticholinergic properties of drugs, an increased sensitivity for extrapyramidal symptoms, an increased risk for orthostatic hypotension and ECG changes, and possible paradoxical reactions to benzodiazepines (Lader and Morton 1991), which include depression, with or without suicidal tendencies, phobias, aggressiveness, violent behaviour, and symptoms misdiagnosed as psychosis. Thus, treatment with TCAs or benzodiazepines is less favorable, while SSRIs, buspirone and moclobemide appear to be safe.

However, very few randomized controlled studies exist that investigate the treatment of anxiety in the elderly.

- One DBPC trial studied elderly patients aged 65 years and older and showed that pregabalin is efficacious and safe in this population (Montgomery et al. 2006a).
- An analysis of the patients aged 60 years and older from a pooled database of five placebo controlled studies and older indicated that venlafaxine is efficacious in elderly patients with GAD (Katz et al. 2002).
- In a small DBPC study with participants aged 60 and older with a DSM-IV anxiety disorder (mainly generalized anxiety disorder), more patients were improved with citalopram than with placebo (Lenze et al. 2005).

Treatment of patients with cardiovascular disease

TCAs are best avoided in patients with cardiac disease, as they can increase heart rate, increase the QT interval, induce orthostatic hypotension, slow cardiac conduction, and have significant quinidine-like effects on conduction within the myocardium. By contrast, the SSRIs have minimal effects on cardiovascular function and may have potentially beneficial effects on platelet aggregation (Davies et al. 2004; Roose 2003). Potential cardiovascular side effects from venlafaxine and duloxetine must be considered. In a study with depressed patients aged 60 and older, venlafaxine was well tolerated. However, undesirable cardiovascular effects occurred in some of the participants (Johnson et al. 2006). Another study of depressed patients on high dose venlafaxine (mean 346 mg; range 225–525 mg) did not demonstrate any clinical or statistically significant effects on electrocardiographic (ECG) parameters (Mbaya et al. 2007).

Anxiety disorders in severe somatic disease

Patients with cardiovascular, cerebrovascular and endocrine disease may have adequate and reasonable anxiety reactions associated with their somatic disease state. They may also suffer from comorbid primary anxiety disorders. Such anxiety disorders are believed to compound the management and the prognosis of chronic obstructive pulmonary disease (Brenes 2003), coronary artery disease or myocardial infarcation (Bankier et al. 2004; Frasure-Smith and Lesperance 2008; Shen et al. 2008), diabetes mellitus (Anderson et al. 2002) or brain injury (Rogers and Read 2007). An anxiety factor based on four scales measuring psychasthenia, social introversion, phobia, and manifest anxiety independently and prospectively predicted the incidence of myocardial infarction in a study of older men (Shen et al. 2008). A diagnosis of GAD incurred an odds ratio of 2.09 of a major cardiac event within in a 2-year period (Frasure-Smith and Lesperance 2008). Survivors of a traumatic brain injury are susceptible to GAD and PTSD (Rogers and Read 2007). A review of studies of anxiolytic treatments in patients with chronic obstructive pulmonary disease (COPD) and comorbid GAD or panic disorder indicate that such treatment may improve both the physical and mental health (Mikkelsen et al. 2004).

Still, since patients with severe somatic disease are excluded from studies, controlled studies that show robust benefit of anxiolytic therapy on vital variables of the somatic condition (e.g., HbA1c, FEV%, myocardial infarction or stroke) are lacking.

Anxiety symptoms may also be a consequence of medical conditions, such as hyperthyroidism (Bunevicius and Prange 2006).

Future research

For a number of putative anxiolytic compounds currently under development only preclinical or preliminary data exist. These include 5-HT_{1A}-agonists, 5-HT_{2C}-agonists, 5-HT_2-antagonists, 5-HT_3-antagonists, beta-carbolines, sigma ligands, tachykinin receptor antagonists, glutamate receptor agonists, neuropeptide Y agonists, CRH receptor antagonists, natriuretic peptide, and nitroflavanoids.

Conclusions

The recommendations in this guideline are primarily based on randomized, controlled, double-blind

trials. However, controlled studies do not always reflect clinical reality and have their shortcomings, e.g., the exclusion of comorbid, suicidal, or medically ill patients. Moreover, it must be seen critically that some treatment modalities that may be effective in treating anxiety disorders have not yet been investigated in well-controlled trials usually because no financial support is available. Absence of evidence is not the same as evidence of absence of an effect. Nevertheless, without controlled trials as gold standard, any treatment recommendation should be understood as based on educated, but anecdotal evidence.

In summary, due to increased efforts in the systematic clinical evaluation of psychopharmacological agents in the treatment of anxiety in the recent years, a comprehensive database has accrued, so that precise recommendations can be provided for treating the anxiety disorders, OCD and PTSD. In most cases, drug treatment, preferably in combination with non-pharmacological treatments such as cognitive behavioural therapy, may substantially improve quality of life in patients with these disorders.

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